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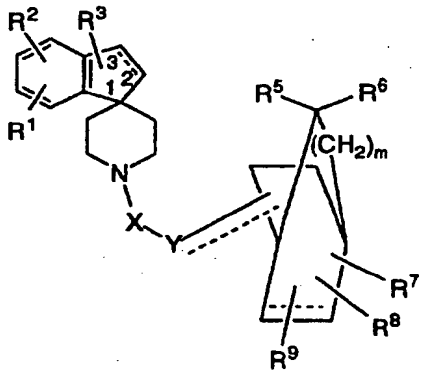


(I)

(57) Abstract

Spirocyclic compounds of formula (I), where m is an integer from zero to one; Y is CH or $CH_2$; and X is C=O, $CH_2$, $PO_2H$, $PO_2Z$, where Z is $C_{1-10}$ alkyl, $SO_2$, CONH, or $SO_2NH$. Such compounds are useful as oxytocin and vasopressin receptor antagonists useful in the treatment of preterm labor, dysmenorrhea and for the stoppage of labor preparatory to cesarean delivery, timing of parturition, uterine hyperactivity, endometriosis, hypertension, congestive heart failure, hyponatremia and cognitive disorders. Also disclosed are pharmaceutical compositions containing these compounds, methods of their use and methods of their preparation.

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TITLE OF THE INVENTION

# PIPERIDINYLCAMPHORSULFONYL OXYTOCIN ANTAGONISTS

## FIELD OF THE INVENTION

This application is a continuation-in-part of U.S. Serial No. 08/153,521, filed November 16, 1993, the contents of which are hereby incorporated by reference, which is a continuation-in-part of U.S. Serial No. 07/954,596, filed September 30, 1992, now abandoned, which is a continuation of U.S. Serial No. 07/759,254, filed September 13, 1991, now abandoned, which is a continuation-in-part of U.S. Serial No. 07/612,344, filed November 13, 1990, now abandoned; the contents of all previous applications are hereby incorporated by reference.

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds generally pharmacologically useful as agents in obstetric and gynecologic therapy. The aforementioned pharmacologic activities are useful in the treatment of mammals. More specifically, the compounds of the present invention can be used in the treatment of preterm labor, stopping labor preparatory to Caesarean delivery, and in the treatment of dysmenorrhea. At the present time, there is a need in the area of obstetric and gynecologic therapy for such agents.

## BACKGROUND OF THE INVENTION

In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus *in utero* is preferred in most instances.

Tocolytic (uterine-relaxing) agents that are currently in use include $\beta_2$-adrenergic agonists, magnesium sulfate and ethanol. Ritodrine, the leading $\beta_2$-adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive

hypoglycemia in the infant). Other $\beta_2$-adrenergic agonists, including terbutaline and albuterol have side effects similar to those of ritodrine. Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest, thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature labor, but it does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

It has been proposed that a selective oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin may be a physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. A selective oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound would be expected to have few, if any, side effects.

The compounds of the present invention are also useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is thought to result from uterine contractions and ischemia, probably

mediated by the effect of prostaglandins produced in the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea than current regimens.

An additional use for the present invention is for the stoppage of labor preparatory to Caesarean delivery. Certain spiroindanylpiperidines and spiroindenylpiperidines are known (U.S. Patents 3,654,287 and 3,666,764), however, they are reported to be useful as anesthetic agents which is quite distinct from the utility of the present invention.

It is, therefore, a purpose of this invention to provide substances which more effectively antagonize the function of oxytocin in disease states in animals, preferably mammals, especially in humans. It is another purpose of this invention to prepare novel compounds which more selectively inhibit oxytocin. It is still another purpose of this invention to provide a method of antagonizing the functions of oxytocin in disease states in mammals. It is also a purpose of this invention to develop a method of preventing or treating oxytocin-related disorders of preterm labor and dysmenorrhea by antagonizing oxytocin.

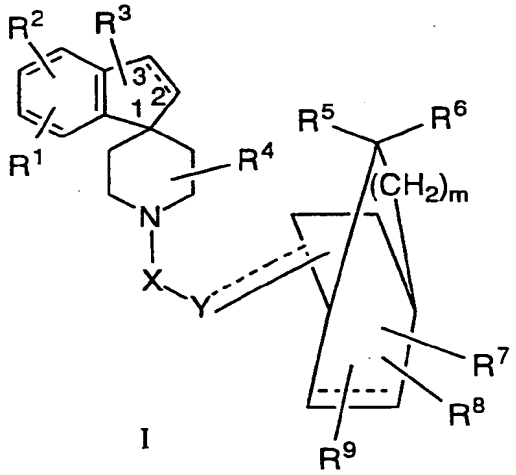
It has now been found that compounds of the present invention are antagonists of oxytocin and bind to the oxytocin receptor. When the oxytocin receptor is bound by the compounds of the present invention, oxytocin is antagonized by being blocked from its receptor and thus being unable to exert its biologic or pharmacologic effects. These compounds are useful in the treatment and prevention of oxytocin-related disorders of animals, preferably mammals and especially humans. These disorders are primarily preterm labor and dysmenorrhea. The compounds would also find usefulness for stoppage of labor preparatory to Caesarean delivery. Additionally, such compounds are useful in inducing contraception in mammals inasmuch as oxytocin antagonists have now been shown to inhibit the release of oxytocin-stimulated luteinizing hormone (LH) by anterior pituitary cells.

Compounds of the present invention are also inhibitors of vasopressin and can bind to the vasopressin receptor. These compounds are useful in inducing vasodilation, treating hypertension, inducing diuresis and inhibiting platelet agglutination.

Additionally, it has now been found that the compounds of the present invention are balanced oxytocin and vasopressin antagonists useful for treating preterm labor and dysmenorrhea.

## SUMMARY OF THE INVENTION

The compounds and their pharmaceutically acceptable salts and esters of the present invention are those of the general structural formula I




I

wherein

X is

$\overset{O}{\overset{\|}{C}}$,

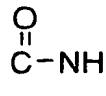
$CH_2$,

$PO_2H$,

$PO_2Z$ where Z is $C_{1-10}$ alkyl,

$SO_2$,

$SO_2NH$ or



Y is absent or is
CH or
$CH_2$;

m is an integer of from zero to one;
n is an integer of from zero to five;
p is an integer of from zero to five;
q is an integer of from zero to five;

$R^1$ and $R^2$ are each independently
hydrogen,
halogen,
hydroxy,
$C_{1-10}$ alkyl,
$C_{1-10}$ alkoxy or
trifluoromethyl;

$R^3$ is
hydrogen,
halogen,
hydroxy or
oxo with the proviso that when $R^3$ is oxo then the 2,3 bond is saturated;

R4 is
hydrogen,
phenyl, or
$C_{1-10}$ alkyl,

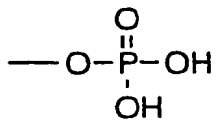
$R^5$ and $R^6$ are independently
hydrogen,

$C_{1-10}$ alkyl or
$C_{1-10}$ hydroxyalkyl; or

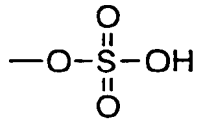
$R^5$ and $R^6$ together are
oxo or
unsubstituted or substituted $C_{3-6}$ cycloalkyl, where said substituents are
hydroxy,
$C_{1-10}$ alkyl,
$C_{1-10}$ hydroxyalkyl,
$C_{1-10}$ alkoxy or
$C_{1-3}$ alkoxyalkoxyalkoxyalkyl;

$R^7$and $R^8$ are independently
hydrogen or
hydroxyl;

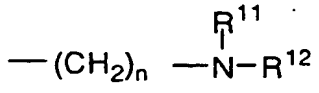
$R^9$ is
$C_{7-10}$ alkoxy,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkoxycarbonylalkylaminocarbonyl,
cyano,



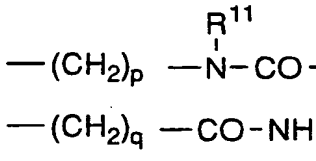
,
$C_{1-10}$ alkyl substituted phosphonate,



,
$C_{1-10}$ alkyl substituted sulfonate,



,



unsubstituted or substituted $C_{1-10}$ alkyl where said substituent is

$R^{10}$; or

$R^7$ and $R^8$ are, together with the carbons to which they are attached, joined to form a 5-membered hetercyclic ring containing 2 hetero atoms where said hetero atoms are N and O;

$R^{10}$ is

hydroxyl,
carboxyl,
$C_{1-10}$ alkoxy,
$C_{1-10}$ alkoxycarbonyl,
$R^{15}$ or
cyano;

$R^{11}$ is

hydrogen,
$C_{1-10}$ alkyl,
$C_{1-10}$ carboxyalkyl or
$C_{1-10}$ alkoxycarbonylalkyl;

$R^{12}$ is

hydrogen,
$C_{1-10}$ alkylsulfonyl,
$C_{1-10}$ alkarylsulfonyl,
$C_{1-10}$ aralkylsulfonyl,
$C_{1-10}$ alkoxyarylsulfonyl,
aminosulfonyl,
$C_{1-10}$ alkylaminosulfonyl,
$C_{1-10}$ dialkylaminosulfonyl,

unsubstituted or substituted C4-15 cycloalkylalkyl, bicycloalkyl or tricycloalkyl where said substituent is
oxo or
sulfonyl substituted by unsubstituted or substituted C7-15 cycloalkyl, bicycloalkyl or tricycloalkyl where said substituents are
oxo,
oxime or
hydroxy;

$R^{13}$ is
amino,
C1-10 alkylamino,
C1-10 alkyl which is unsubstituted or mono- or di-substituted by $R^{16}$,
C2-10 alkenyl which is unsubstituted or substituted by $R^{16}$,
phenyl substituted by $R^{17}$,
unsubstituted or substituted C3-8 cycloalkyl where said substituents are
C1-10 alkyl or
carboxy,
N disubstituted by C1-10 alkyl,
unsubstituted or substituted C7-15 bicycloalkyl or tricycloalkyl where said substituent is
carboxy,
C1-10 alkoxy or
$R^{18}$;

$R^{14}$ is
C1-10 alkyl,
C1-10 aminoalkyl,
C1-10 alkoxycarbonylalkyl, or
C1-10 carboxyalkyl,

$R^{15}$ is

unsubstituted or substituted 5 membered heterocyclic rings containing 1 hetero atom where said hetero atom is N and said substituents are

oxo,
amino,
$C_{1-10}$ alkylamino,
$C_{1-10}$ carboxyalkylcarbonylamino,
$C_{1-10}$ dicarboxyalkylamino or
$C_{1-10}$ alkyloxycarbonylalkylamino;

$R^{16}$ is

unsubstituted or substituted $C_{4-8}$ cycloalkyl where said substituents are

hydroxy or
carboxy,
$C_{10-15}$ bi- or tricycloalkyl,
halogen,
hydroxy,
carboxy,
oxo,
oxime,
$C_{1-10}$ alkylthio,
$C_{1-10}$ alkylsulfinyl,
$C_{1-10}$ alkylsulfonyl,
$C_{1-10}$ alkoxycarbonyl,
$R^{20}$,
$R^{21}$,
amino,
aminocarbonyl,
$C_{1-10}$ dialkylaminocarbonyl,
$C_{1-10}$ alkylamino,
$C_{1-10}$ dialkylamino,
$C_{1-10}$ alkylcarbamate,

$C_{1-10}$ alkylcarbonate,
$C_{1-10}$ alkylureide,
$C_{1-10}$ aralkylcarbamate,
unsubstituted or substituted aryloxy where said substituents are
amino,
$C_{1-10}$ alkyl or
$C_{1-10}$ aminoalkyl,
$C_{1-10}$ aralkoxy,
unsubstituted or substituted $C_{1-10}$ alkaryloxy where said substituent is
$C_{1-10}$ alkylcarbamate,
N disubstituted by $C_{1-10}$ alkyl and $C_{1-10}$ carboxyalkyl or
N tri-substituted by two $C_{1-10}$ alkyls and by $C_{1-10}$ alkoxycarbonylalkyl with the proviso that a trifluoroacetic acid counterion be present;

$R^{17}$ is
amino,
halogen,
$C_{1-10}$ alkyl,
$C_{1-10}$ alkoxy,
nitro,
phenylcarbonyl or
unsubstituted or substituted 5 membered heterocyclic rings containing 1 hetero atom where said hetero atom is O and wherein said substituent is
oxo;

$R^{18}$ is unsubstituted or substituted heterocyclic rings selected from
azetidinyl,
pyrrolidinyl,
pyrrolyl,
piperidinyl,

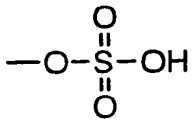
piperizinyl,
pyridinyl,
pyrimidinyl,
tetrahydrofuranyl,
furanyl,
dioxolanyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrooxazolyl; where said substituents are one or more of
oxo,
hydroxy,
carboxy,
amino,
$C_{1-10}$ carboxyalkyl,
$C_{1-10}$ alkyl,
$C_{1-10}$ alkoxy,
$C_{1-10}$ aralkoxy,
$C_{1-10}$ alkaryloxy,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkoxycarbonylamino,
$C_{1-10}$ alkoxycarbonylalkyl,
$C_{1-10}$ aralkoxycarbonyl or
substituted or unsubstituted phenyl where said substituents are
$C_{1-5}$ alkyl,
carboxy or
halogen;

$R^{20}$ is unsubstituted or substituted heterocyclic rings selected from
azetidinyl,
pyrrolidinyl,
pyrrolyl,
tetrahydroimidazolyl,
imidazolyl,

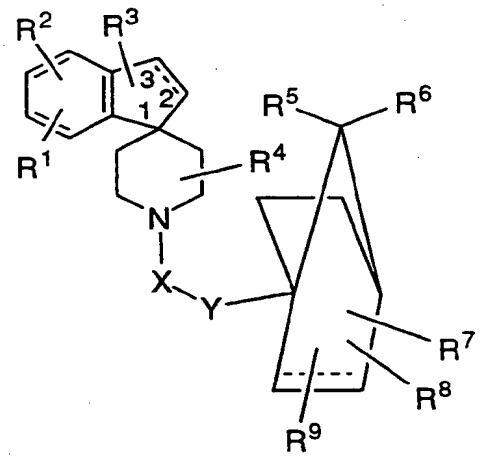
tetrazolyl,
piperidinyl,
pyridinyl,
hexahydroazepinyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrothiazinyl; where said substituents are one or more of
$C_{1-10}$ alkyl,
$C_{1-10}$ aralkyl,
$C_{1-10}$ aralkoxy,
$C_{1-10}$ alkaryl,
amino,
$C_{1-10}$ alkylamino,
$C_{1-10}$ dialkylamino,
oxo,
oxime,
fused phenyl,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkylcarbonate,
$C_{1-10}$ alkylureide,
$C_{1-10}$ alkylcarbamate, or
unsubstituted or substituted 5-membered heterocyclic rings having 1 hetero atom where said hetero atom is N and said substituent is one or more of
oxo or
fused phenyl;

$R^{21}$ is
unsubstituted or substituted phenyl where said substituents are
halogen,
$C_{1-10}$ alkyl,
$C_{1-10}$ carboxyalkyl,
$C_{1-10}$ alkoxy,

5- or 6-membered heterocyclic rings having 1 or 2 hetero atoms where said hetero atoms are N or S,
hydroxy,
carboxy or



In one embodiment of the instant invention are compounds of the formula



wherein
X is

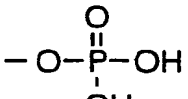
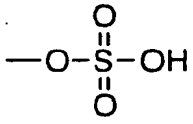
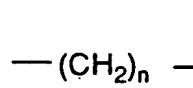
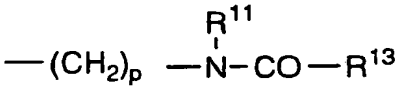
C,
$CH_2$,
$PO_2H$,
$PO_2Z$ where Z is $C_{1-10}$ alkyl, or
$SO_2$;

$R^1$ and $R^2$ are each independently
hydrogen,
halogen or
$C_{1-10}$ alkyl;

R4 is
hydrogen or
phenyl;

R5 and R6 are independently
hydrogen or
C1-10 alkyl; or

R5 and R6 together are
oxo or
unsubstituted or substituted C3-6 cycloalkyl, where said substituents are
hydroxy,
C1-10 hydroxyalkyl or
C1-3 alkoxyalkoxyalkoxyalkyl;

R9 is
C7-10 alkoxy,
C1-10 alkoxycarbonyl,
C1-10 alkoxycarbonylalkylaminocarbonyl,
C1-10 alkyl substituted  ,
 ,
phosphonate,
C1-10 alkyl substituted sulfonate,
 ,
 ,
unsubstituted or substituted C1-10 alkyl where said substituent is

$R^{10}$; or

$R^7$ and $R^8$ are, together with the carbons to which they are attached, joined to form a 5-membered heterocyclic ring containing 2 hetero atoms where said hetero atoms are N and O;

$R^{12}$ is
hydrogen,
$C_{1-10}$ alkylsulfonyl,
$C_{1-10}$ alkarylsulfonyl,
$C_{1-10}$ alkoxyarylsulfonyl,
aminosulfonyl,
$C_{1-10}$ dialkylaminosulfonyl,
unsubstituted or substituted $C_{3-15}$ cycloalkylalkyl where said substituent is
oxo or
sulfonyl substituted by unsubstituted or substituted $C_{3-15}$ cycloalkyl where said substituent is
oxo;

$R^{14}$ is
$C_{1-10}$ alkyl,
$C_{1-10}$ aminoalkyl or
$C_{1-10}$ alkoxycarbonylalkyl;

$R^{16}$ is
unsubstituted or substituted $C_{5-6}$ cycloalkyl where said substituent is
hydroxy,
$C_{10-15}$ tricycloalkyl,
halogen,
hydroxy,
carboxy,
oxo,

$C_{1-10}$ alkylthio,
$C_{1-10}$ alkylsulfonyl,
$C_{1-10}$ alkoxycarbonyl,
$R^{20}$,
$R^{21}$,
amino,
$C_{1-10}$ alkylamino,
$C_{1-10}$ dialkylamino,
$C_{1-10}$ alkylcarbamate,
$C_{1-10}$ aralkylcarbamate,
unsubstituted or substituted aryloxy where said substituents are
amino,
$C_{1-10}$ alkyl or
$C_{1-10}$ aminoalkyl,
$C_{1-10}$ aralkoxy,
unsubstituted or substituted $C_{1-10}$ alkaryloxy where said substituent is
$C_{1-10}$ alkyl carbamate,
N disubstituted by $C_{1-10}$ alkyl and $C_{1-10}$ carboxyalkyl; or
N tri-substituted by two $C_{1-10}$ alkyls and by $C_{1-10}$ alkoxycarbonylalkyl with the proviso that a counterion be present from the group consisting of $C_{1-5}$ halogenated carboxylic acids;

$R^{18}$ is unsubstituted or substituted heterocyclic rings selected from
azetidinyl,
pyrrolidinyl,
pyrrolyl,
piperidinyl,
piperizinyl,
pyridinyl,
pyrimidinyl,
tetrahydrofuranyl,

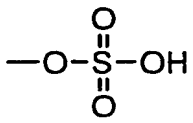
furanyl,
dioxolanyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrooxazolyl, where said substituents are one or more of
oxo,
hydroxy,
carboxy,
C1-10 carboxyalkyl,
C1-10 alkyl,
C1-10 alkoxy,
C1-10 aralkoxy,
C1-10 alkoxycarbonyl,
C1-10 alkoxycarbonylalkyl or
C1-10 aralkoxycarbonyl;

$R^{20}$ is unsubstituted or substituted heterocyclic rings selected from
hexahydroazepinyl,
pyrrolidinyl,
pyrrolyl,
tetrahydroimidazolyl,
imidazolyl,
tetrazolyl,
piperidinyl,
pyridinyl,
azetidinyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrothiazinyl; where said substituents are one or more of
C1-10 alkyl,
C1-10 aralkyl,
C1-10 aralkoxy,
amino,
oxo,

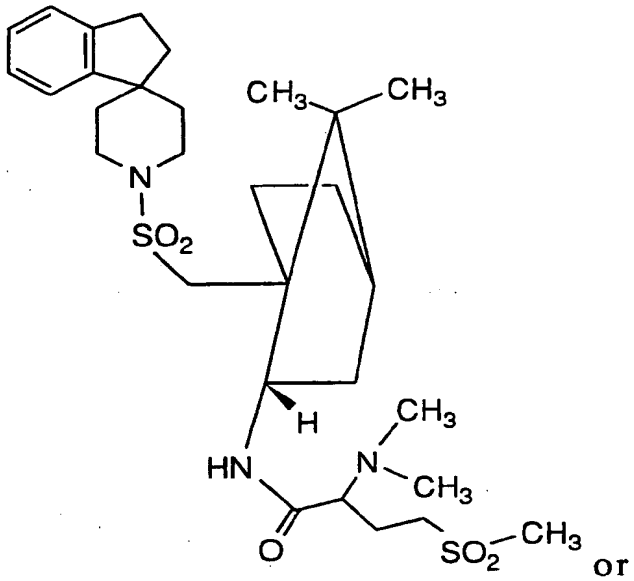
fused phenyl,
C1-10 alkoxycarbonyl,
C1-10 alkylcarbamate, or
unsubstituted or substituted 5-membered heterocyclic rings having 1 hetero atom where said hetero atom is N and said substituent is
oxo or
fused phenyl;

$R^{21}$ is

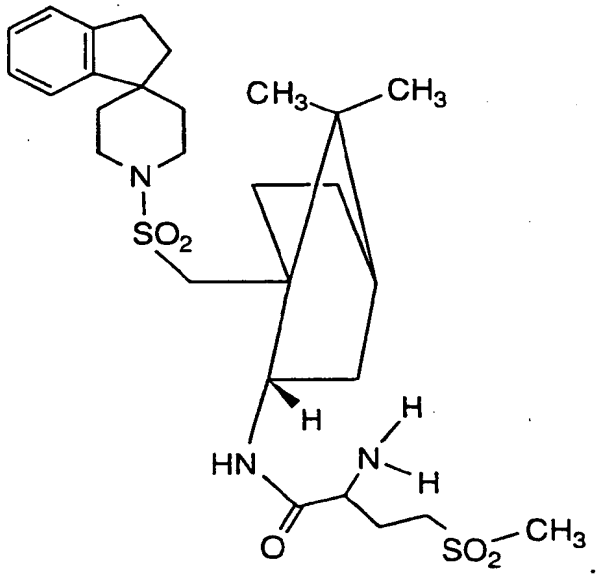
unsubstituted or substituted phenyl where said substituents are
C1-10 alkyl,
C1-10 carboxyalkyl,
C1-10 alkoxy,
5- or 6-membered heterocyclic rings having 1 or 2 hetero atoms where said hetero atoms are N or S,
hydroxy,
carboxy or



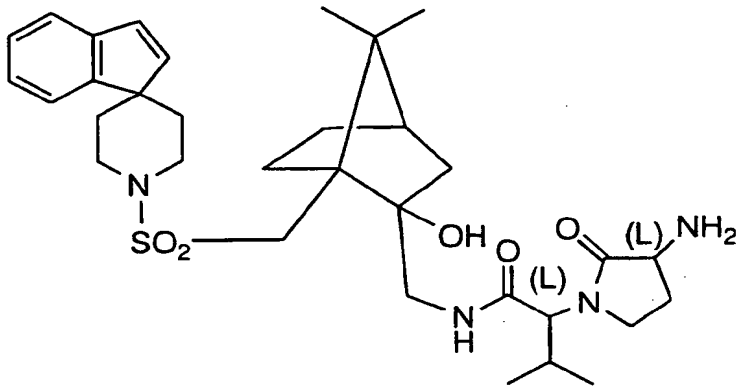
In a class are the compounds selected from



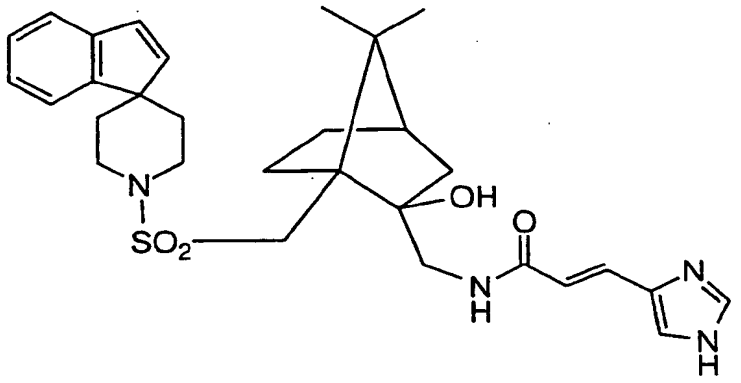
or



In another class are the compounds selected from



or



Illustrative of the invention is a pharmaceutical composition, comprising a compound of formula I in a pharmacologically effective amount for antagonizing the binding of oxytocin to its receptor site, and a pharmaceutically acceptable carrier.

Illustrations of the present invention include methods of antagonizing the binding of oxytocin to its receptor site, preventing preterm labor, treating dysmenorrhea, and stopping labor preparatory to cesarean delivery, in a mammal in need thereof, comprising the step of administering to the mammal a pharmacologically effective amount of a compound of formula I.

Exemplifying the invention are methods of antagonizing vasopressin from binding to its receptor site, inducing vasodilation, treating hypertension, inducing diuresis, and inhibiting platelet agglutination, in a mammal in need thereof comprising the step of

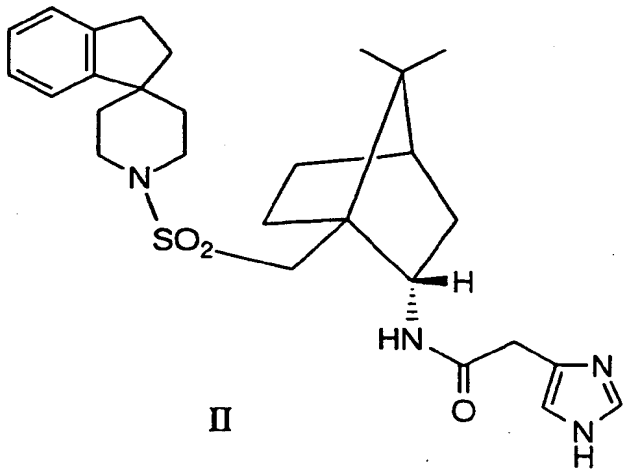
administering to the mammal a pharmacologically effective amount of a compound of formula I.

An example of the invention is a method of increasing fertility and embryonic survival in a farm animal comprising administering to the farm animal a pharmacologically effective amount of a compound of the present invention.

Further illustrating the invention is a method for improving survival of a farm animal neonate comprising controlling timing of parturition to effect delivery of the neonate during daylight hours by administering to a farm animal which is expected to deliver the neonate within 24 hours a pharmacologically effective amount of a compound of the present invention.

Another illustration of the invention is a method of controlling the timing of estrus in a farm animal, comprising administering to the farm animal a pharmacologically effective amount of a compound of the present invention.

Also included in the instant invention is a compound of the formula II




II

and the pharmaceutically acceptable salts thereof.

An embodiment of the invention is a pharmaceutical composition, comprising the compound of formula II in a

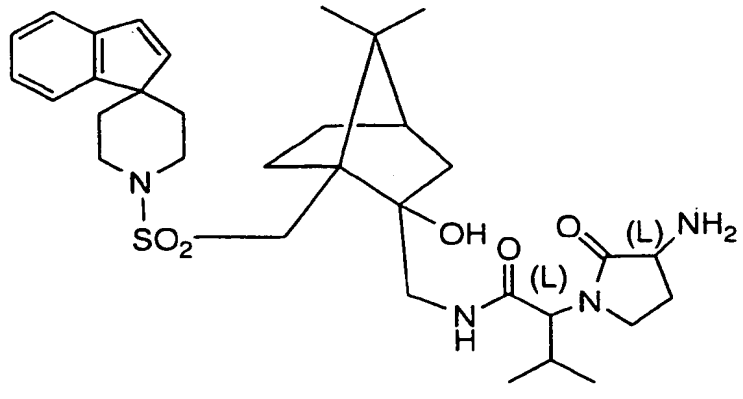
pharmacologically effective amount for antagonizing the binding of oxytocin to its receptor site, and a pharmaceutically acceptable carrier.

Illustrative of the invention are methods of antagonizing the binding of oxytocin to its receptor site, preventing preterm labor, treating dysmenorrhea, and stopping labor preparatory to cesarean delivery, in a mammal in need thereof, comprising the step of administering to the mammal a pharmacologically effective amount of a compound of formula II.

Also encompassed in the instant invention are methods of treating preterm labor and dysmenorrhea in a mammal in need thereof, comprising administering to the mammal a pharmacologically effective amount of a compound which binds to a human oxytocin receptor with a binding affinity which is no more than ten-fold higher or ten-fold lower than the binding affinity with which the compound binds to a human arginine-vasopressin-V1a (AVP-V1a) receptor.

More particularly illustrating the the invention are the methods of treating preterm labor and dysmenorrhea, wherein the compound binds to the human oxytocin receptor with a binding affinity which is no more than five-fold higher or five-fold lower than the binding affinity with which the compound binds to the human AVP-V1a receptor.

Exemplifying the invention are the methods of treating preterm labor and dysmenorrhea, wherein the compound is selected from

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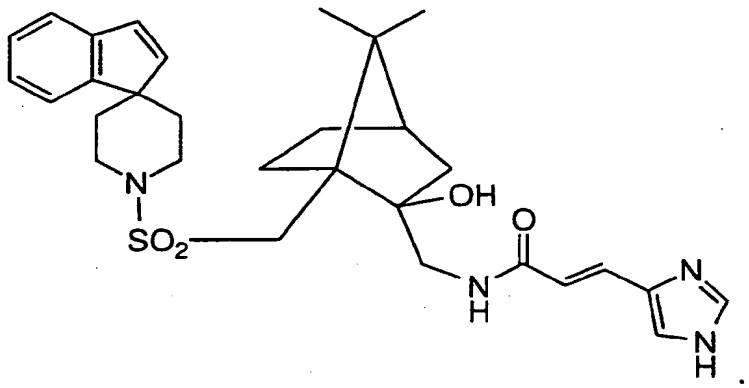


Salts and esters encompassed within the term "pharmaceutically acceptable salts and esters" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts and esters include the following:

Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate ,Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, Tannate, Tartrate, Teoclate ,Tosylate, Triethiodide and Valerate.

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range.

The term "lower alkyl" shall mean straight or branched chain alkanes of one to five total carbon atoms, or any number within this range.

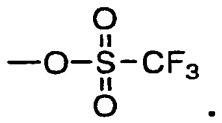
The term "alkenyl" shall mean straight or branched chain alkenes with one or more degrees of unsaturation at any position on the chain, of two to ten total carbon atoms, or any number within this range.

The term "alkynyl" shall mean straight or branched chain alkynes with one or more degrees of unsaturation at any position on the chain, of two to ten total carbon atoms, or any number within this range.

The term "aryl" shall mean phenyl, naphthyl or fluorenyl.

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms.

The term "trihaloalkylsulfonyloxo" shall mean the substituent



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Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. aralkoxyaryloxy), it shall be interpreted as including those limitations given above for "alkyl" or "aryl." Designated numbers of carbon atoms (e.g. $C_{1-10}$) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The term "oxo" shall refer to the substituent =O.

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

The term "Caesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

As used herein, the definition of each expression when it occurs more than once in any structure, can be independent of its definition elsewhere in the same structure.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent.

Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

The compounds of the present invention, may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

Oxytocin (OT) and arginine vasopressin (AVP) are structurally related peptide hormones of the pituitary gland having distinct biological functions. OT is released from the pituitary in response to stimuli related to parturition (e.g., labor, suckling of the neonate). Circulating OT then stimulates uterine activity to promote labor and delivery and contracts mammary gland myoepithelium to elicit milk-letdown postpartum. AVP, on the other hand, is secreted into the bloodstream by disturbances in hemostasis such as reduced blood pressure or blood volume and/or increased plasma osmolality. AVP acts to correct these imbalances by enhancing peripheral vascular resistance and by promoting water reabsorption by the kidney. These effects of AVP are mediated by distinct receptors of the vascular smooth muscle (AVP-$V_{1a}$ receptors) and kidney (AVP-$V_2$ receptors),

respectively. AVP-$V_{1a}$ receptors are also located in uterine smooth muscle to cause contraction and on platelets to mediate aggregation. By contrast, the contractile responses of the uterus and mammary glands to OT appear to be transduced by a separate, single receptor subtype. A third, relatively obscure vasopressin receptor subtype, AVP-$V_{1b}$, has been identified in the pituitary gland where it mediates the stimulatory effects of AVP on adrenocorticotrophic hormone (ACTH) release. The human OT, AVP-$V_{1a}$ and AVP-$V_2$ receptors have recently been cloned and expressed.

The ability of the compounds of the present invention to antagonize oxytocin makes these compounds useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein oxytocin may be involved. Examples of such disorders include preterm labor and dysmenorrhea. These compounds may also find usefulness for stoppage of labor preparatory to Cesarean delivery.

The oxytocin antagonist compounds of the present invention are also useful for improving reproductive efficiency in farm animals. In certain farm animals (e.g., sheep, cattle, swine and goats), the beginning of the estrous cycle is typically marked by behavioral estrus when the female animal accepts the male for mating. Ovulation of the ovarian follicle occurs shortly after onset of estrus and cells in the follicle give rise to the corpus luteum. The cells that form the corpus luteum produce progesterone and they also produce oxytocin. The secretion of oxytocin from the corpus luteum and/or pituitary acts on the uterine endometrium to stimulate the secretion of prostaglandins (in particular PGF) which, in turn, causes the regression of the corpus luteum of the ovary. PGF is, therefore, the luteolytic hormone. In the cycling animal (i.e., where mating and fertilization have not occurred), destruction of the corpus luteum removes the source of progesterone which is key to the preparation of the uterus for pregnancy. The presence of a viable conceptus (i.e., the embryo and its associated membranes) is necessary to prevent the luteolytic process. In fact, the first key signal that the conceptus must produce is the one to prevent

regression of the corpus luteum (i.e., the maternal recognition of pregnancy signal). Thus, in the animal where mating and fertilization have occurred, the conceptus secretes a factor that antagonizes the action of oxytocin to induce luteolysis. This results in maintenance of a functioning corpus luteum and the continued secretion of progesterone which is obligatory to the initiation of pregnancy.

Administration of an oxytocin antagonist of the present invention at this critical period after fertilization (i.e., just prior to or during the period of maternal recognition of pregnancy) supplements the natural signal from the conceptus (i.e., maternal recognition of pregnancy) to prolong corpus luteal function. The result is to increase pregnancy rates by enhancing the chances of impregnation through a reduction in embryonic loss. Thus, to improve fertility in a farm animal, a mated animal, for example, a mated ewe, is treated with an oxytocin antagonist compound beginning on between day 10 to day 15 after onset of estrus. The oxytocin antagonist compound is administered to the mated animal for a period of one day to three weeks, preferably one week to three weeks, most preferably one week to two weeks.

The compounds of the present invention are also useful in farm animals for controlling the timing of parturition so that delivery of neonates occurs during the daytime. Approximately 80% of livestock are delivered at night and up to 5 to 10% of newborns die because the deliveries are not monitored properly. An oxytocin antagonist compound of the present invention administered to the mother on the evening before expected delivery delays parturition so that the delivery occurs during the daylight hours. By delaying the timing of parturition, proper monitoring of the delivery and the neonates is ensured, resulting in increased survival rates of the newborns.

In addition, the oxytocin antagonists of the instant invention can also be used to control the timing of estrus in a cycling farm animal by preventing luteal regression. An oxytocin antagonist compound of the instant invention is administered to a cycling farm animal prior to expected estrus to prevent regression of the corpus luteum. Daily

administration of the compound retards estrus until administration of the compound ceases. Preferably, the oxytocin antagonist compound is administered at least 1 day prior to expected estrus. By delaying estrus in a group of farm animals, a farmer can synchronize estrus among the group to provide time and cost savings in farm management.

The compounds of the present invention also bind to the vasopressin receptors and are therefore useful as vasopressin antagonists. Vasopressin antagonists are useful in the treatment or prevention of disease states involving vasopressin disorders, including their use as diuretics and their use in congestive heart failure.

It has now been found that compounds of the present invention are balanced oxytocin and vasopressin antagonists useful for treating preterm labor and dysmenorrhea. The terms "balanced oxytocin and vasopressin antagonist(s)," "balanced oxytocin/vasopressin compound(s)," and "balanced oxytocin/arginine-vasopressin (AVP)-$V_{1a}$ compound(s)," as used herein, are defined as a compound which has a ten-fold or less separation between the binding affinity of the compound for a human oxytocin receptor and the binding affinity of the compound for a human AVP-$V_{1a}$ receptor. Preferably, there is a five-fold or less separation between the binding affinities of the compound to the oxytocin and AVP-$V_{1a}$ receptors. It is believed that a balanced oxytocin/vasopressin compound will provide a more effective treatment for preterm labor and dysmenorrhea. The fact that oxytocin receptors are up-regulated in the uterine myometrium during labor and before and during menstruation (AVP-$V_{1a}$ receptors are also present but are not up-regulated), the observation that the uterus responds to both oxytocin and AVP and that the sensitivity of the uterus to the contractile effects of oxytocin is highest during labor and menstruation, and the fact that oxytocin/AVP-stimulated synthesis of contractile prostaglandins occurs during labor and menstruation indicates that a balanced oxytocin/vasopressin antagonist compound would provide effective treatment for both preterm labor and dysmenorrhea. In addition, it appears that the vasoconstrictor activity of AVP (AVP-$V_{1a}$ response) contributes to uterine ischemia and pain. Thus, balanced

oxytocin/vasopressin compounds, such as the balanced oxytocin/vasopressin compounds disclosed herein, provide a novel approach for the treatment of preterm labor and dysmenorrhea.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a tocolytic agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.3-6.0 gm/day orally. Intravenously, the most preferred doses will range from 0.1 to about 10 mg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the

present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention is also directed to combinations of the compounds of formula I with one or more agents useful in the treatment of oxytocin related disorders such as preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery. For example, the compounds of the instant invention may be effectively administered in combination with effective amounts of other agents used in the treatment of preterm labor, such as antenatal steroids (e.g., dexamethasone). Preferred combinations are simultaneous or alternating treatments of an oxytocin receptor antagonist of the present invention and an antenatal steroid. These combinations have beneficial effects on the neonate by both decreasing uterine activity to prolong gestation and increasing fetal maturation. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating oxytocin related conditions includes in principle any combination with any pharmaceutical composition useful for treating preterm labor, dysmenorrhea or stopping labor prior to cesarean delivery.

The compounds of the instant invention can be prepared readily according to the following reaction schemes and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of

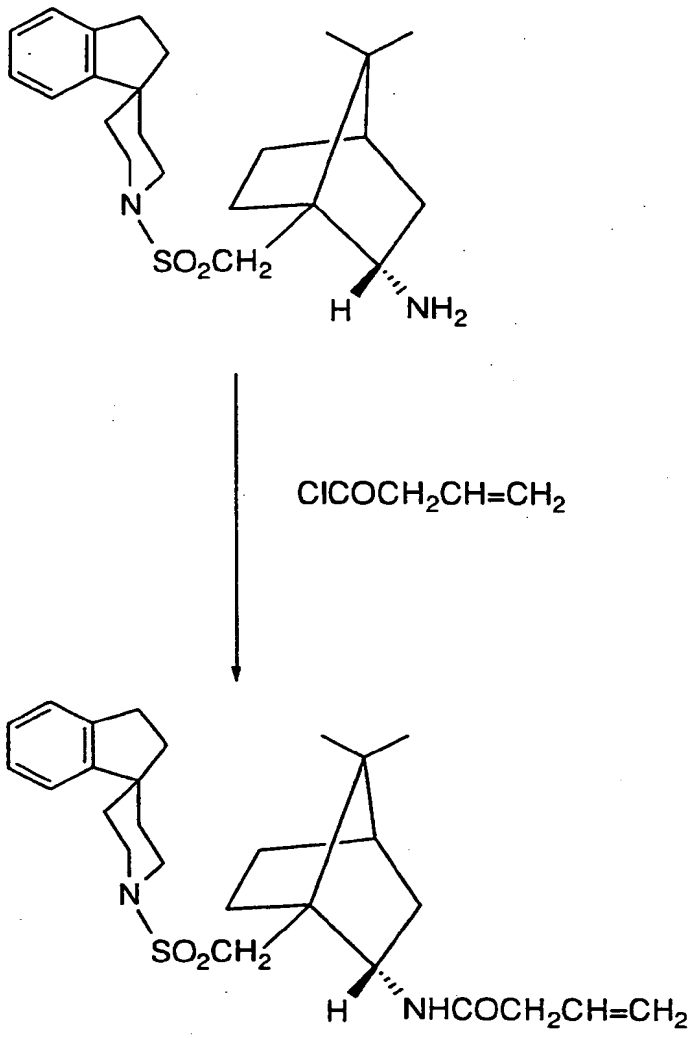
ordinary skill in this art, but are not mentioned in greater detail. Reference can also be made to U.S. Patent No. 5,091,387, issued February 25, 1992, the entire disclosure of which is incorporated by reference. Additional reference can also be made to the method of Matier, et al., J. Org. Chem., Vol. 36, No. 5, 650-654 (1971), the entire disclosure of which is incorporated by reference, on elaboration of indenes and their 2-oxo derivatives to spiropiperidine analogs. Also incorporated by reference is a variant of this procedure described in Matier, et al., J. Org. Chem., Vol. 36, No. 5, 650-654 (1971).

The most preferred compounds of the invention are any or all of those specifically set forth in these Examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

Abbreviations used in the Examples are as follows:

BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
DCM = dichloromethane
DIEA = diisopropylethylamine
DMF = dimethylformamide
EtOAc = ethyl acetate
EtOH = ethanol
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FAB MS = fast atom bombardment mass spectroscopy
HOBT = 1-hydroxybenzotriazole
HPLC = high pressure liquid chromatography
MeOH = methanol
NMR = nuclear magnetic resonance
THF = tetrahydrofuran
TLC = thin layer chromatography

EXAMPLE 1



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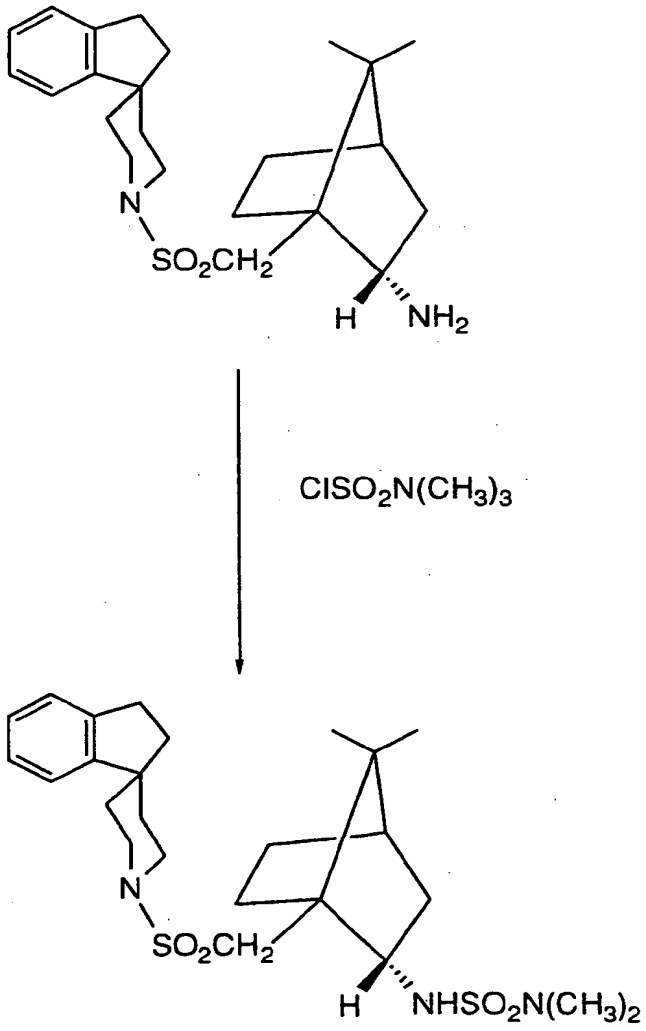

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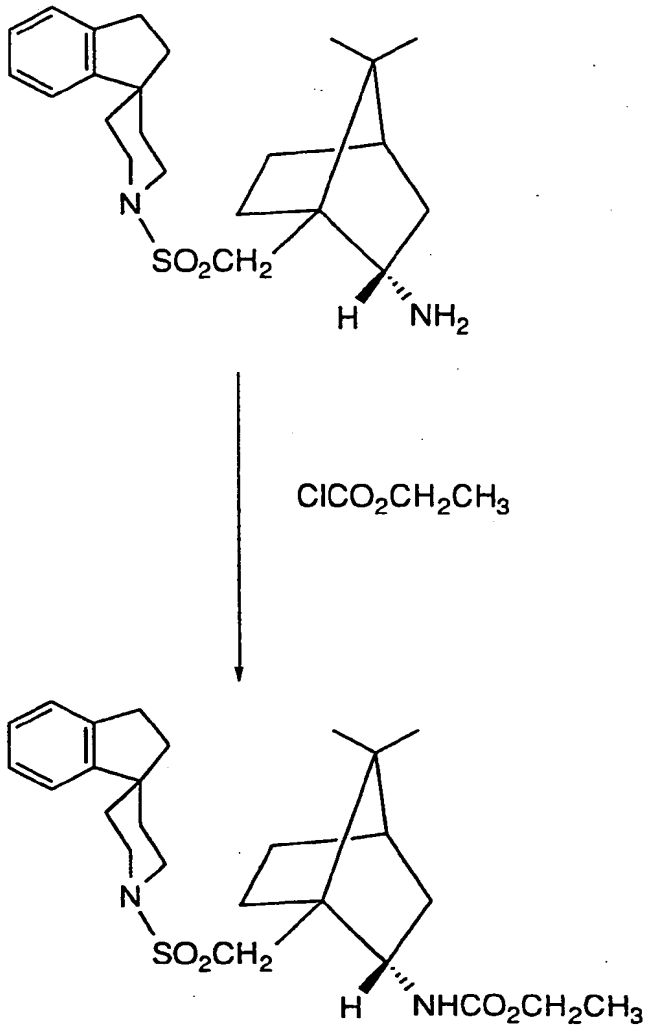

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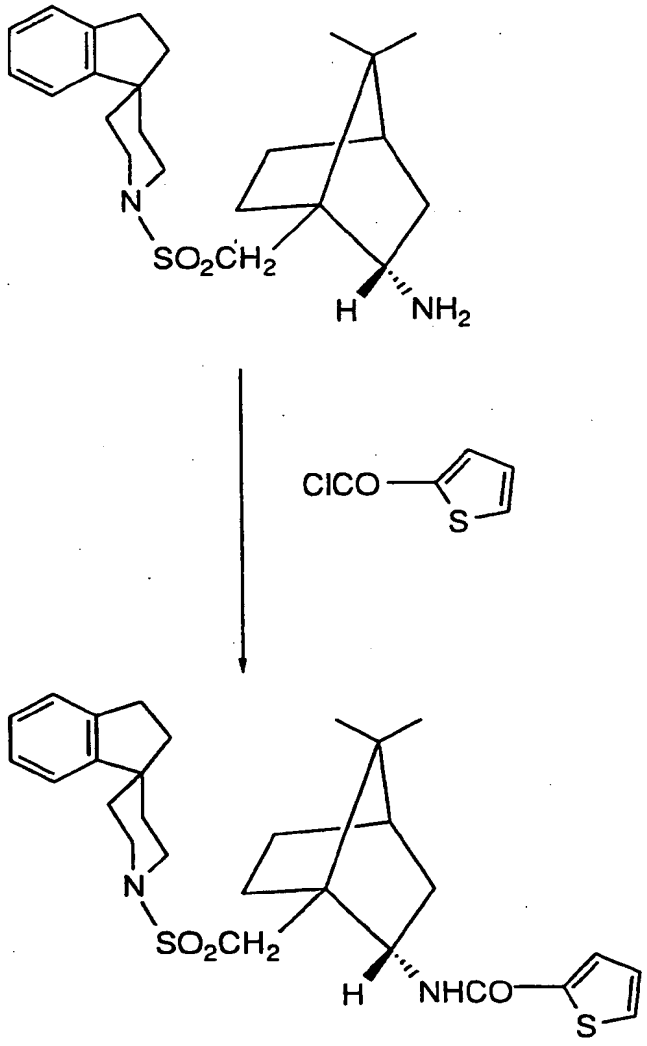

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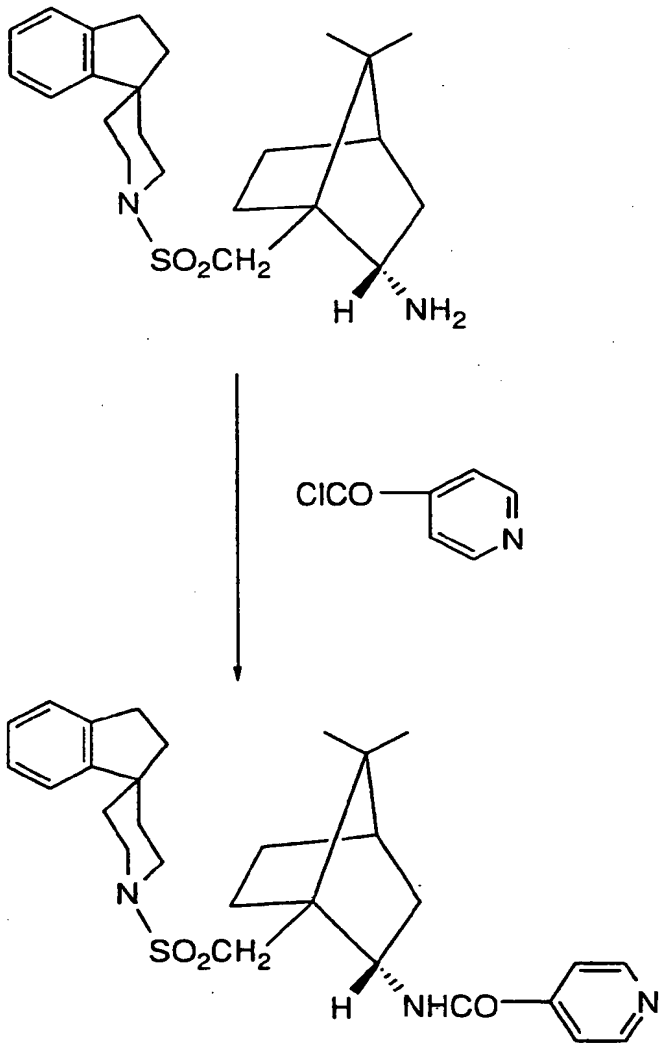

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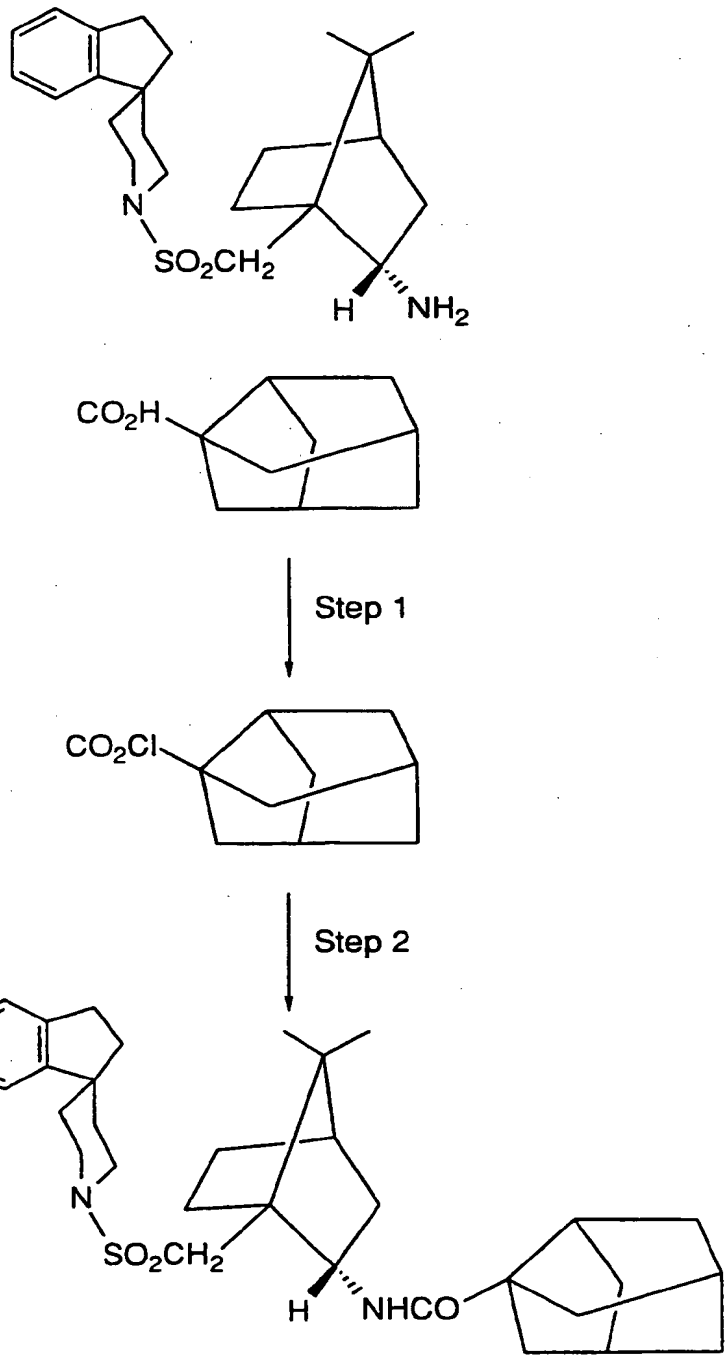

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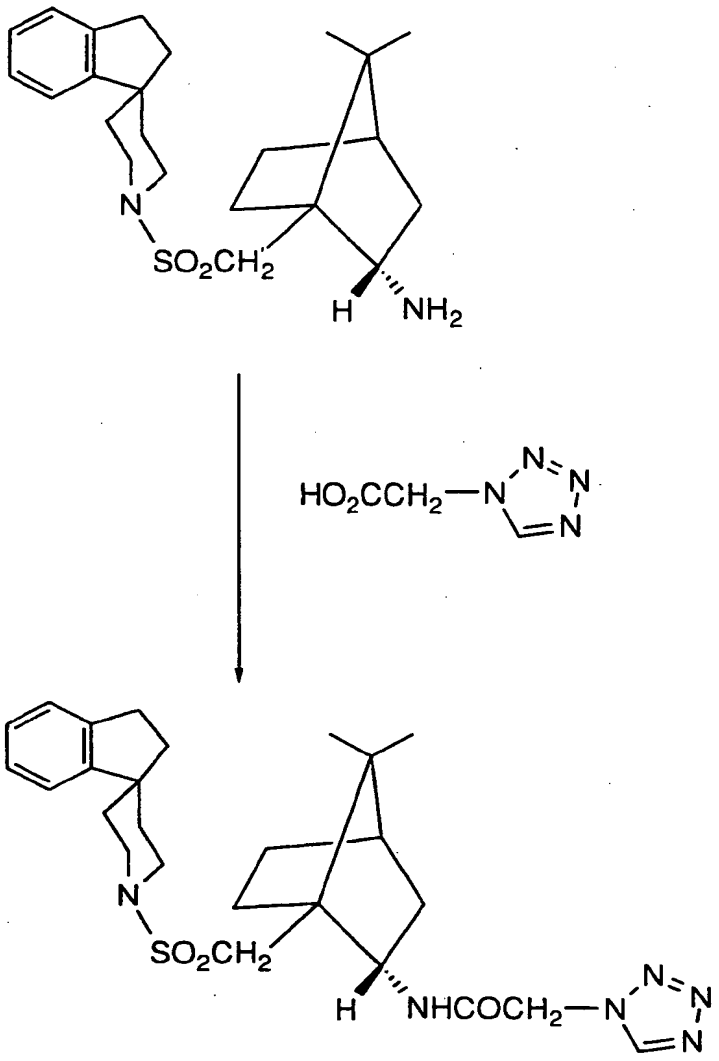
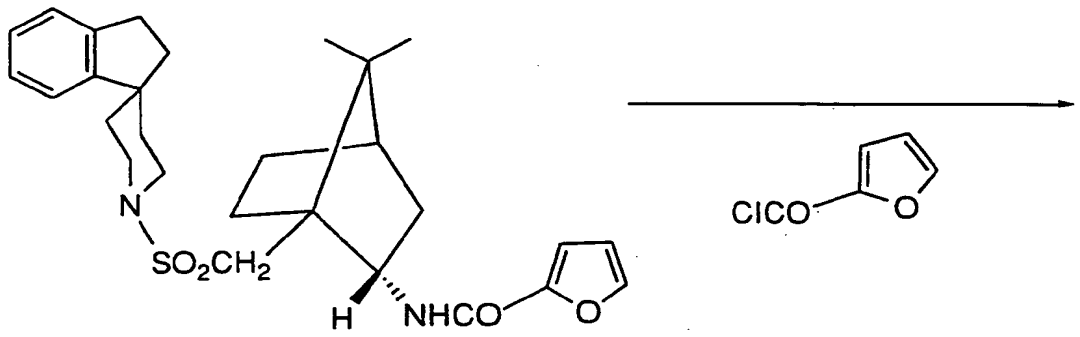
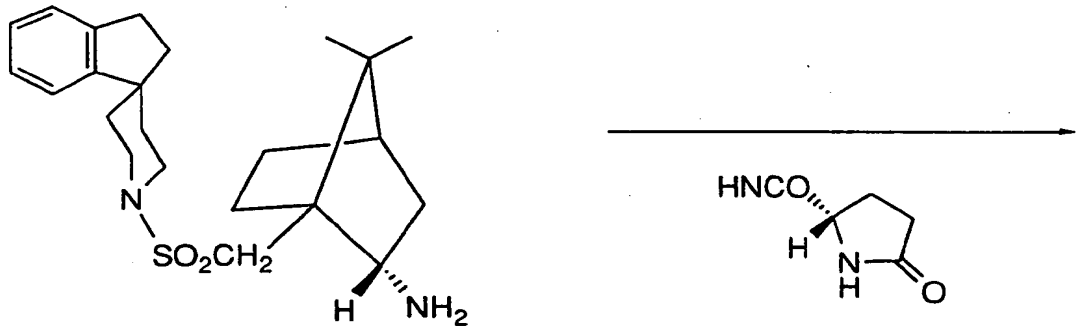
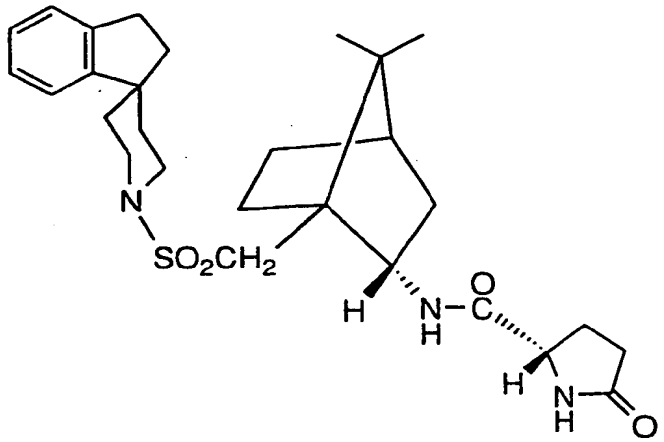


## REACTION SCHEMES, PART 2

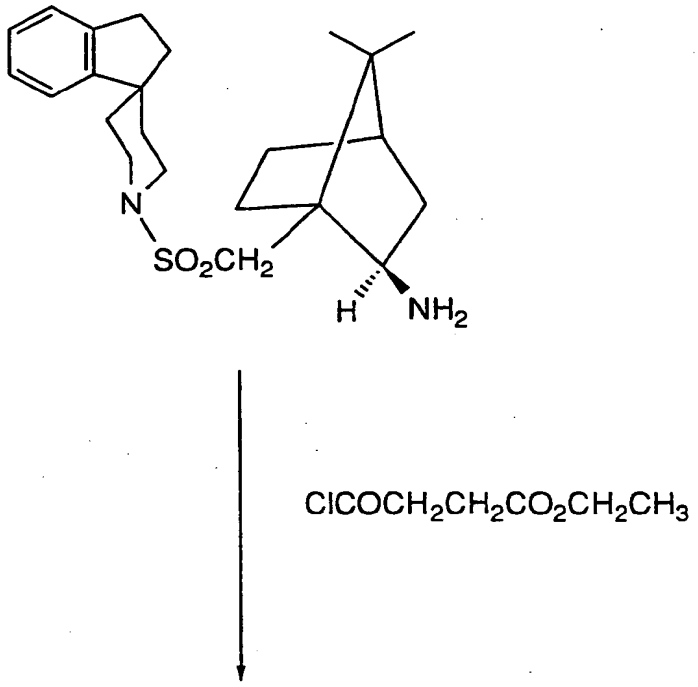


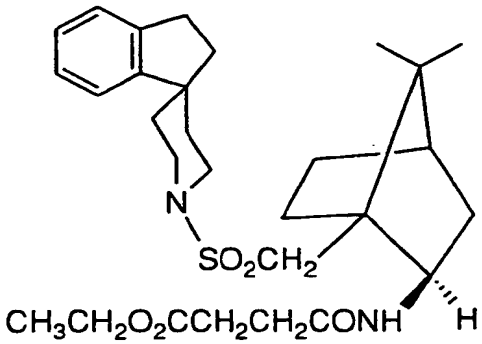

## EXAMPLE 10



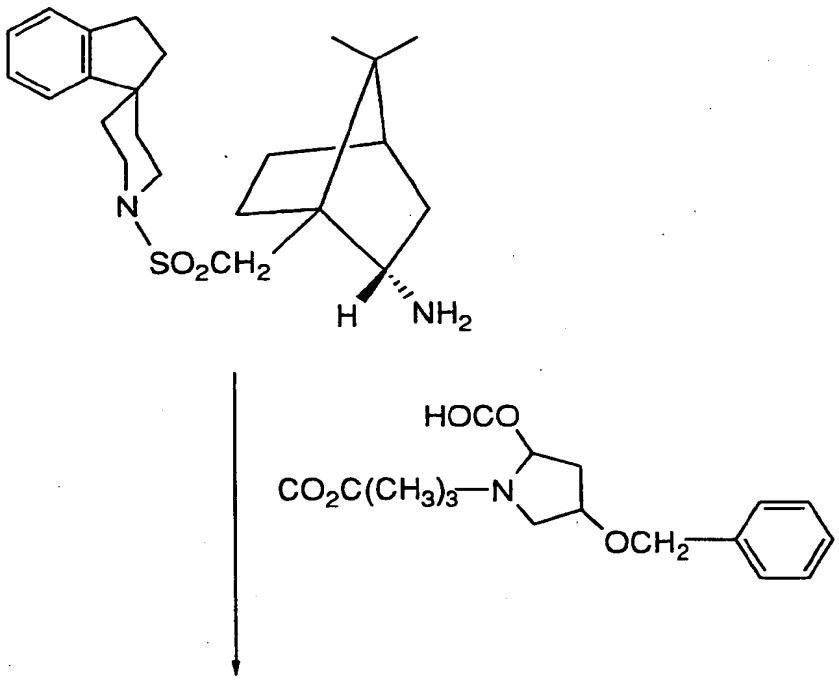
## REACTION SCHEMES, PART 3



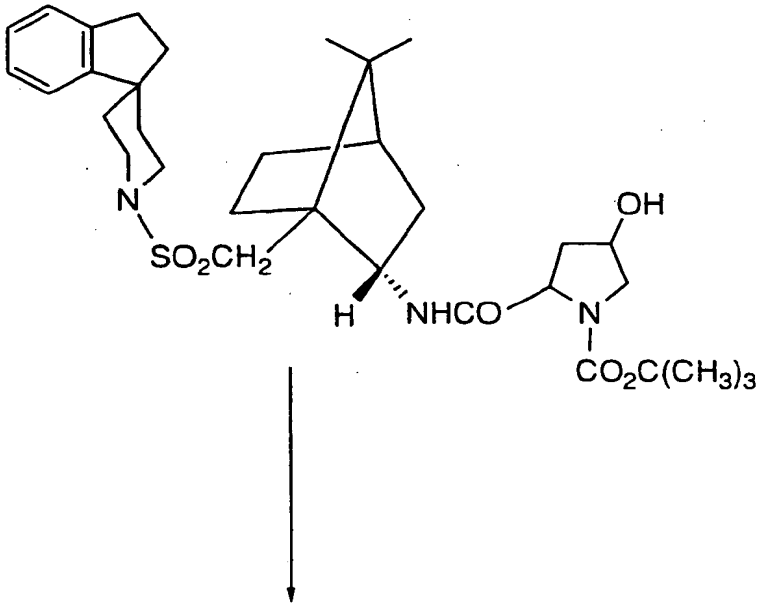

## EXAMPLE 7



REACTION SCHEMES, PART 3 CONT'D

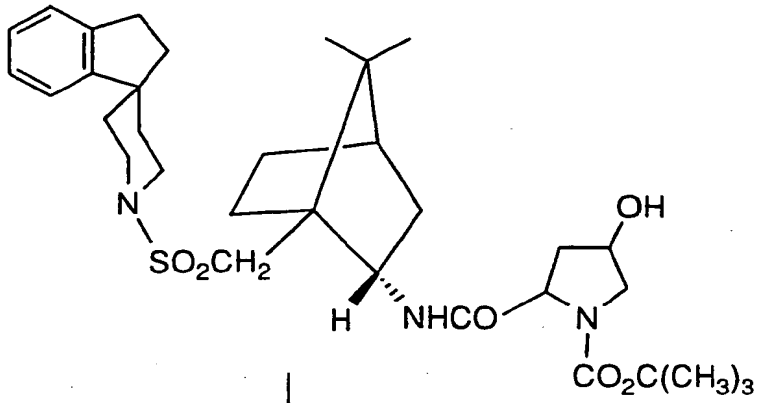



EXAMPLE 11

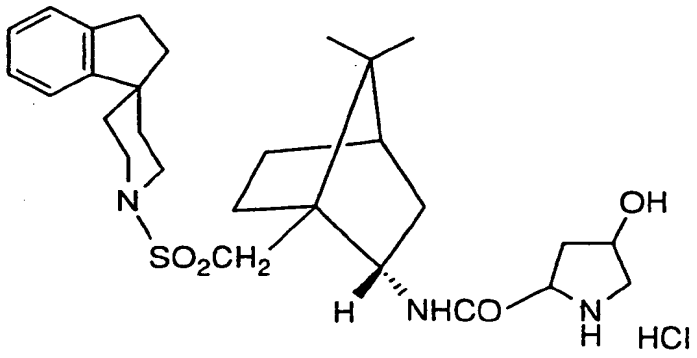


REACTION SCHEMES, PART 3 CONT'D

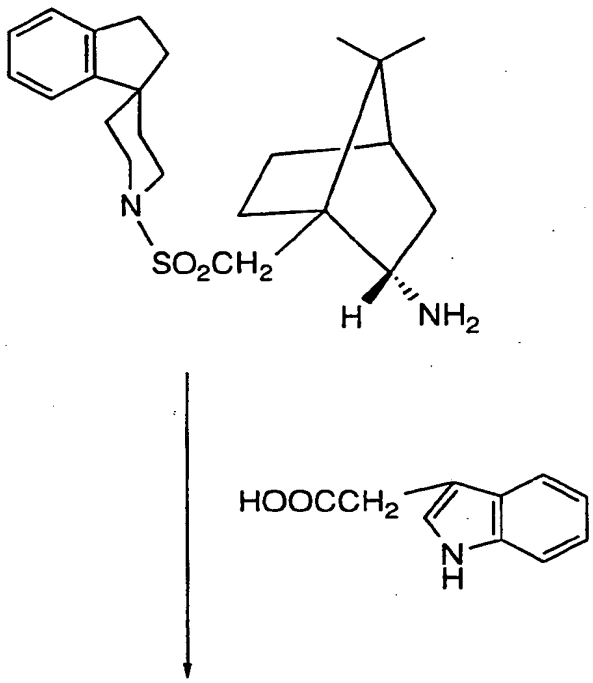
EXAMPLE 12



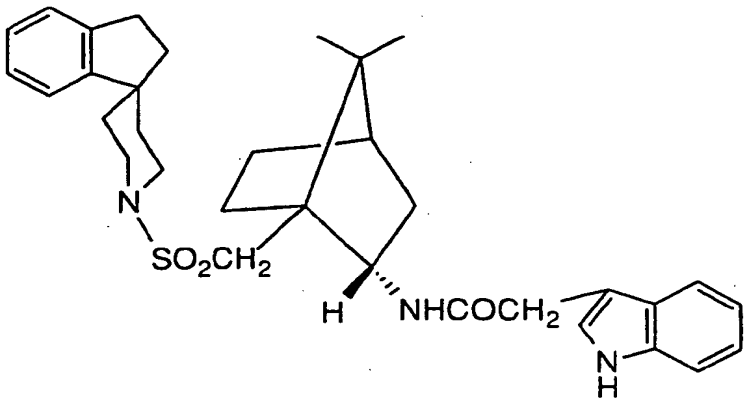

EXAMPLE 13



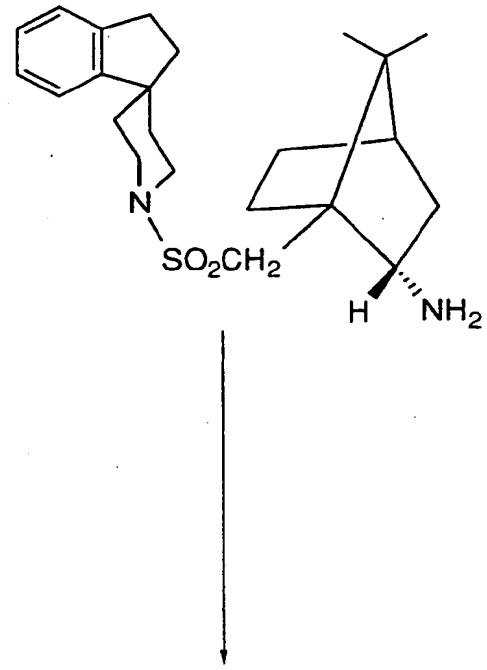
REACTION SCHEMES, PART 3 CONT'D



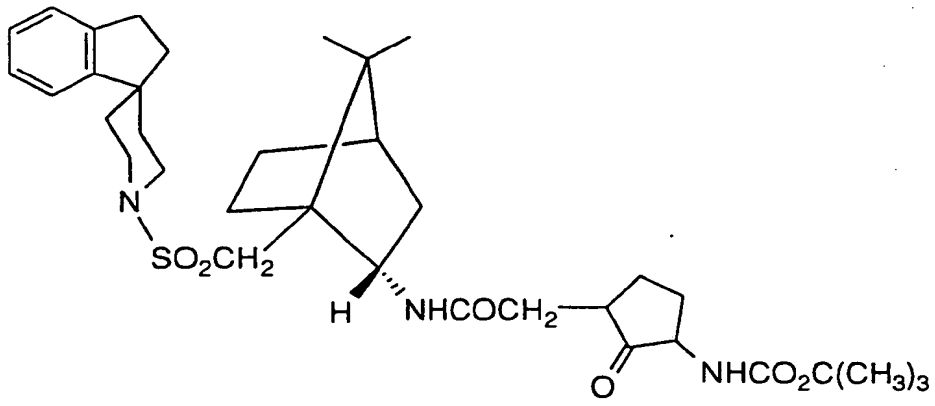

EXAMPLE 14



## REACTION SCHEMES, PART 4



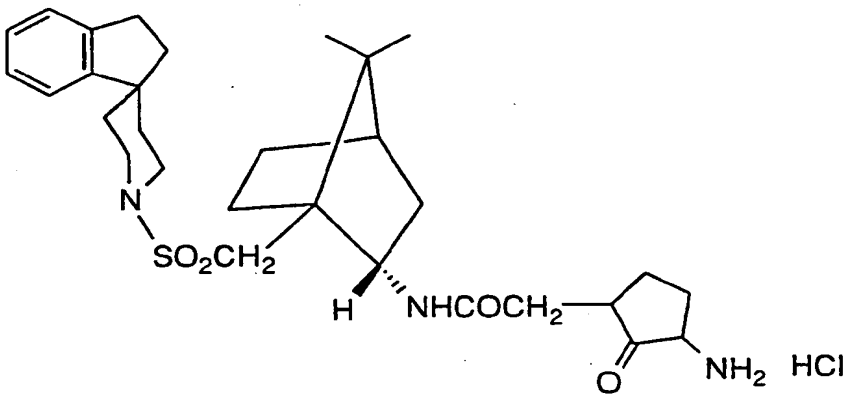

## EXAMPLE 15



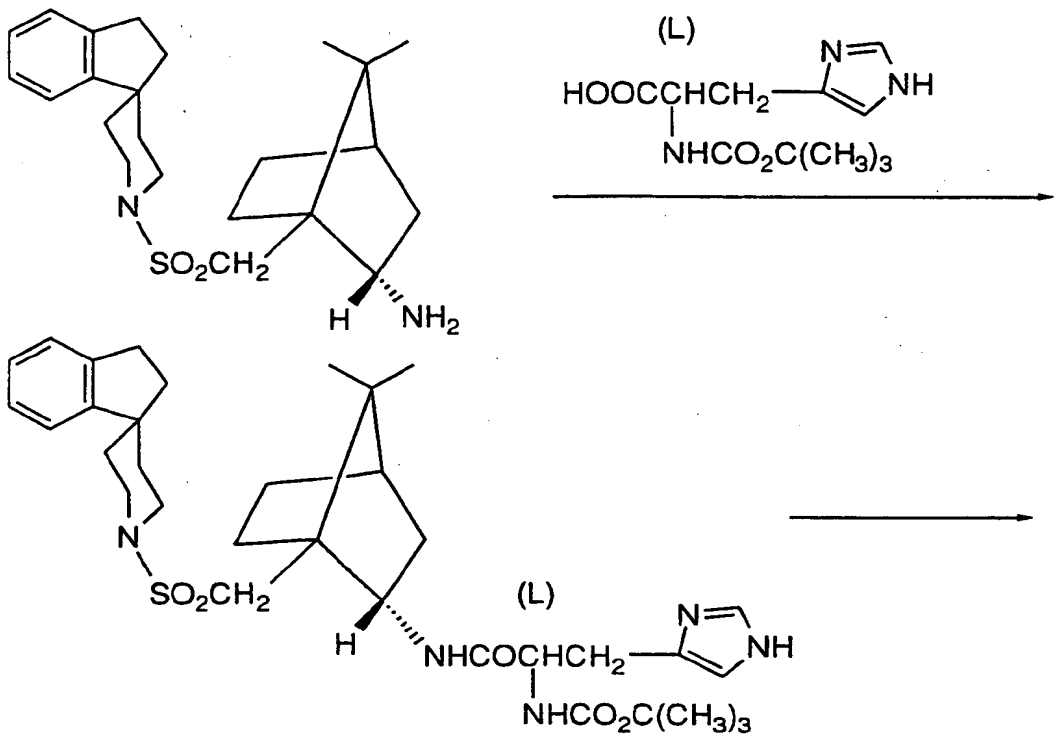
REACTION SCHEMES, PART 4 CONT'D



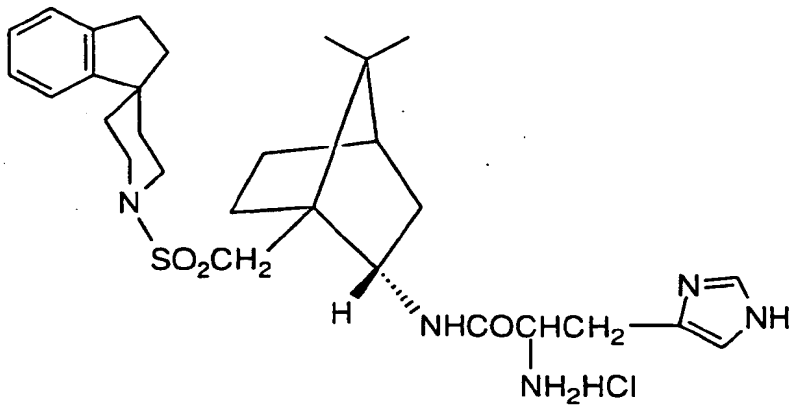
EXAMPLE 16



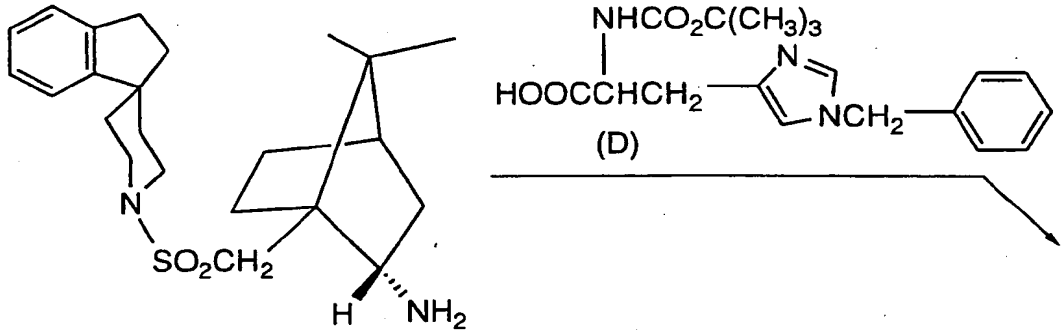
## REACTION SCHEMES, PART 5



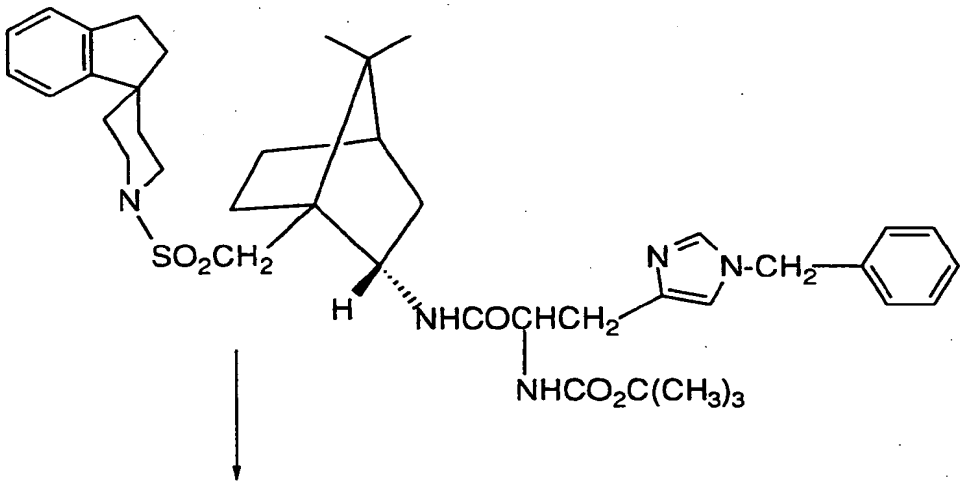

## EXAMPLE 17



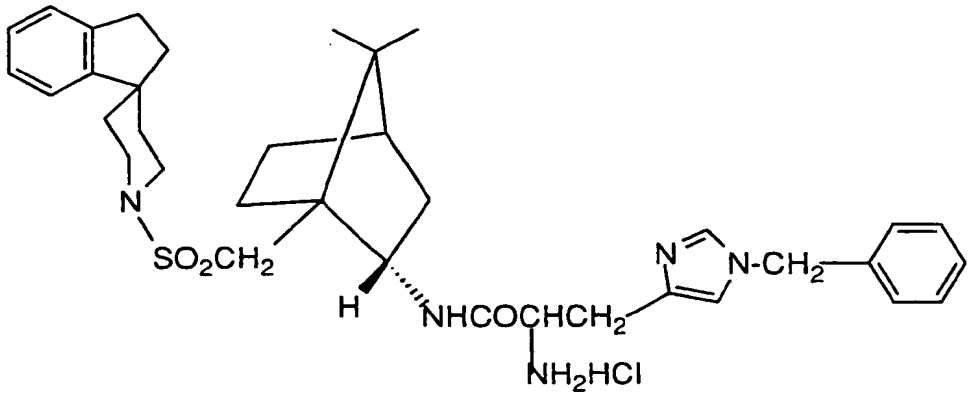
REACTION SCHEMES, PART 5 CONT'D



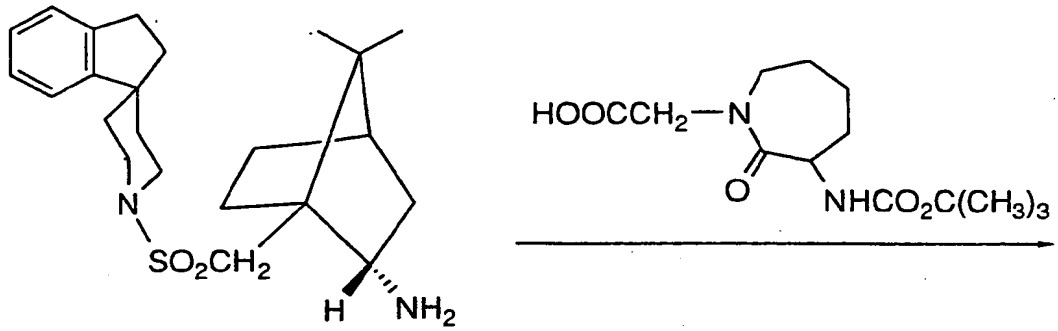

EXAMPLE 18



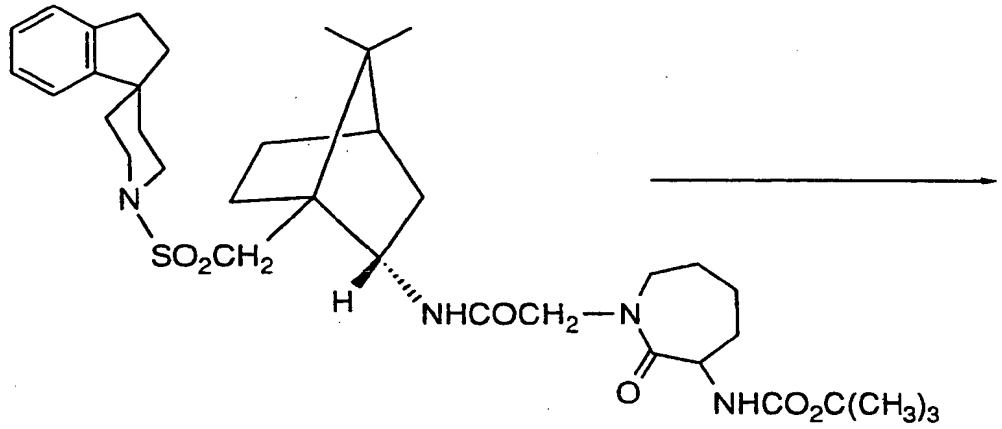

EXAMPLE 19



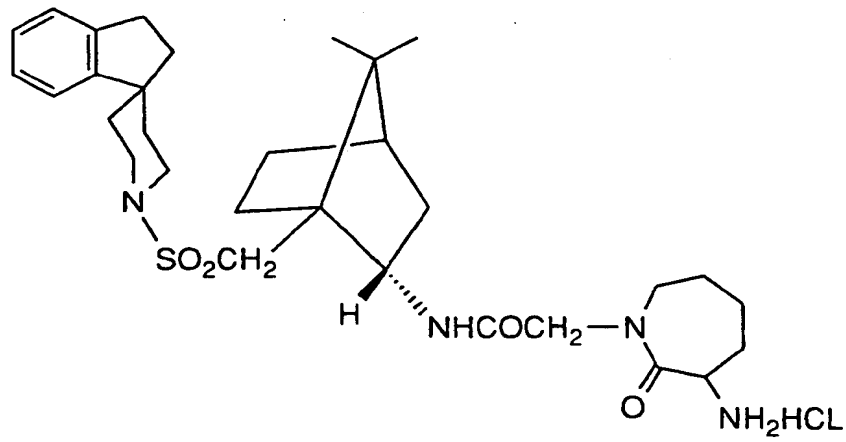
## REACTION SCHEMES, PART 6




## EXAMPLE 20




## EXAMPLE 21

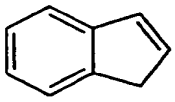


## REACTION SCHEMES, PART 7

$(ClCH_2CH_2)_2NH\ HCl + [(CH_3)_3COCO]_2O$

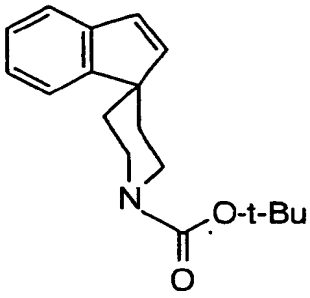
$Et_3N$

$(ClCH_2CH_2)_2NCO_2$-t-Bu



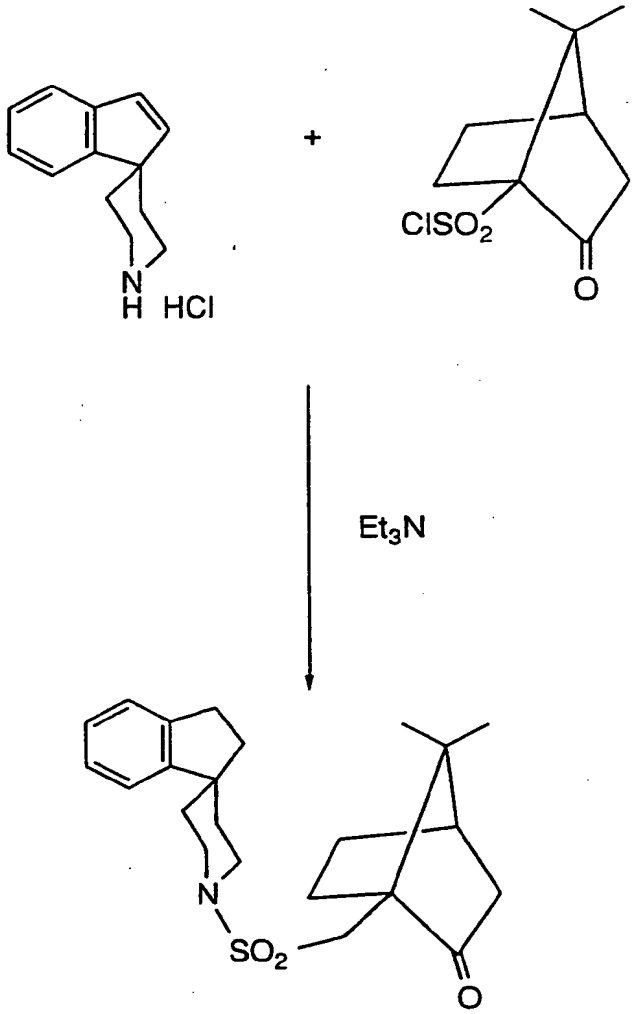
+ $(ClCH_2CH_2)_2NCO_2$-t-Bu

$LiN[Si(CH_3)_3]_2$

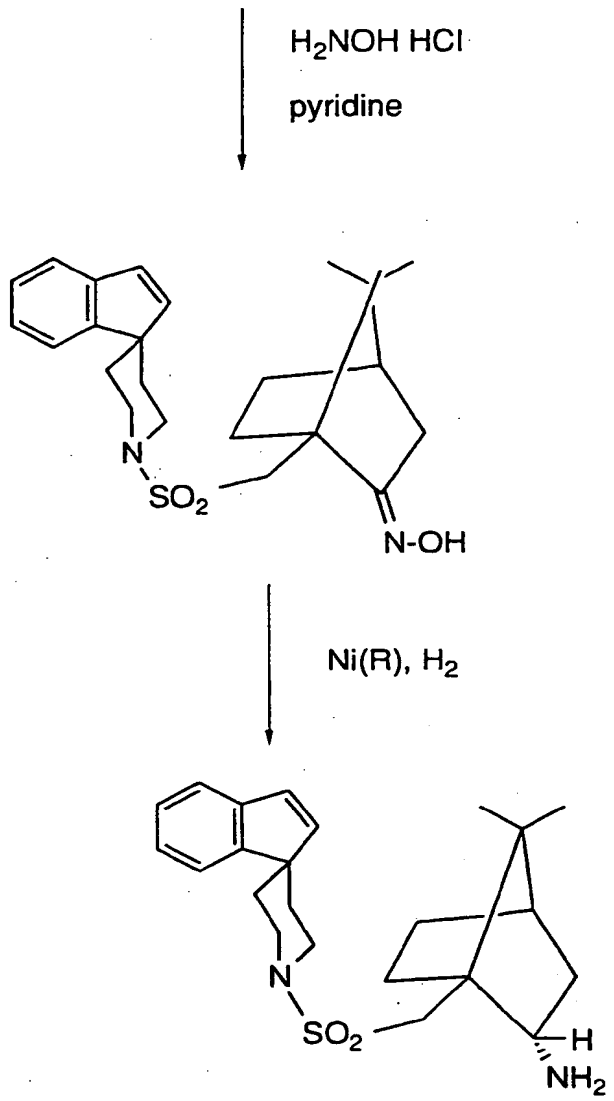



HCl, EtOAc

REACTION SCHEMES, PART 7 CONT'D



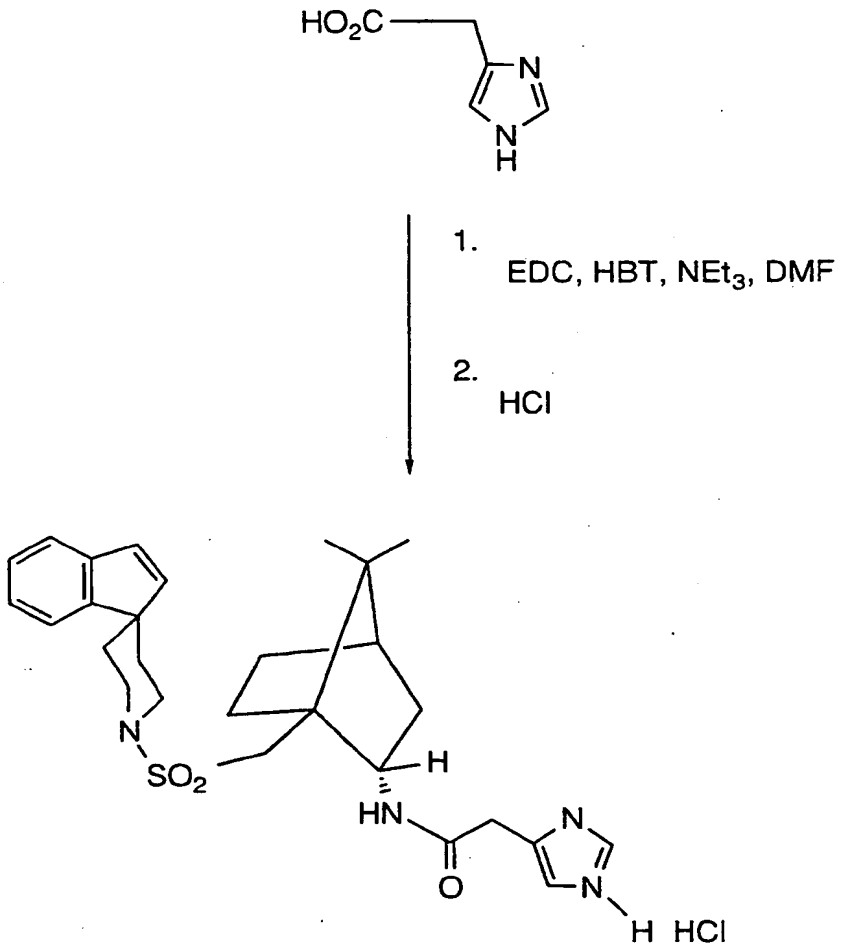
REACTION SCHEMES, PART 7 CONT'D



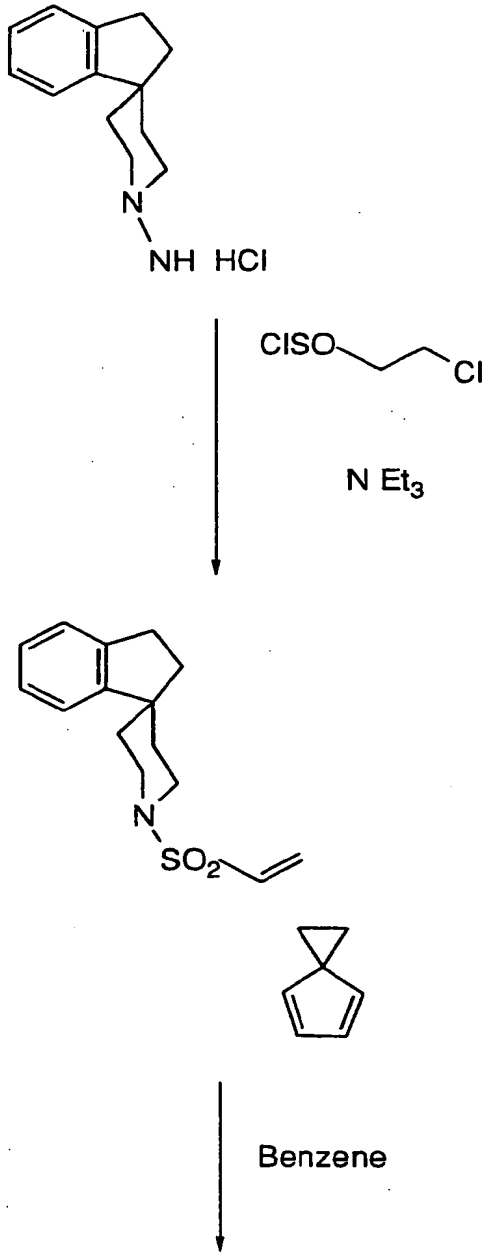

+

Endo Isomer

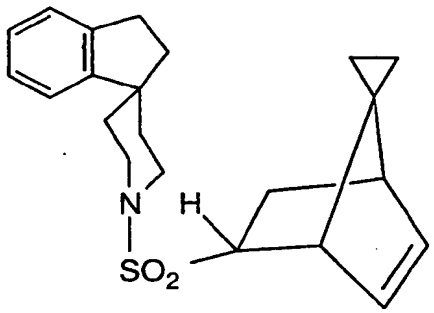
REACTION SCHEMES, PART 7 CONT'D



REACTION SCHEMES, PART 8

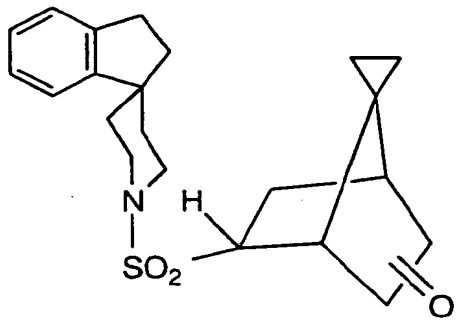


REACTION SCHEMES, PART 8 CONT'D



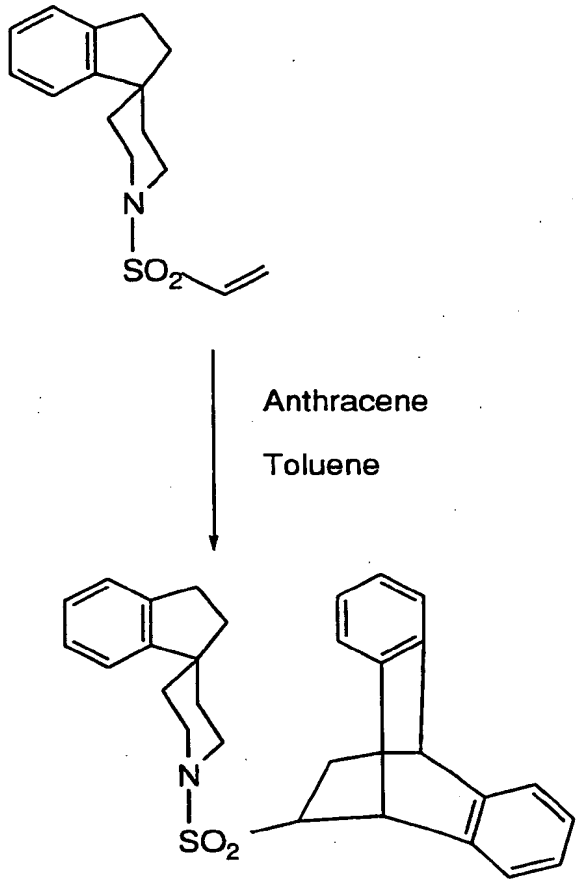

+ TRACE OF EXO ISOMER

1. $BH_3$ THF
   $H_2O_2$, OH
2. pyridinium chlorochromate, $CH_2Cl_2$



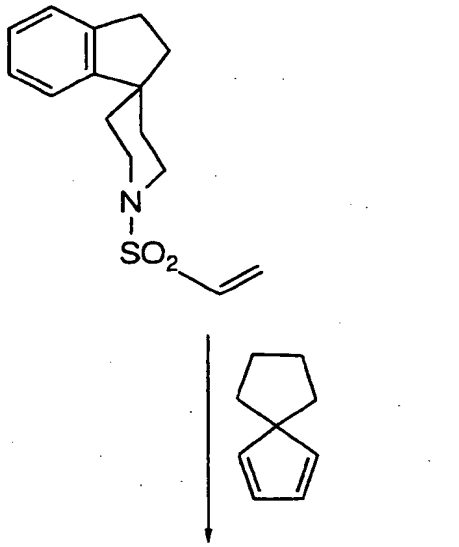

EXAMPLE 31

REACTION SCHEMES, PART 8 CONT'D



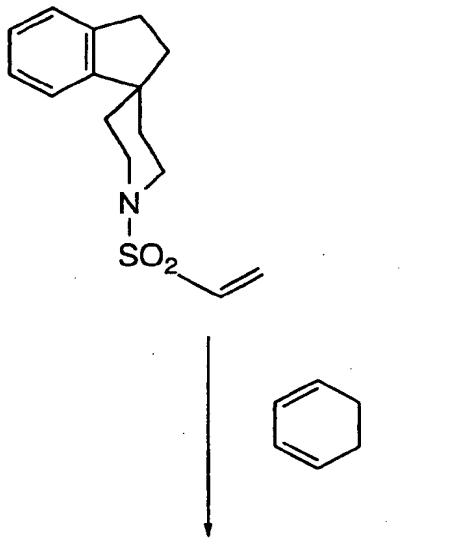

EXAMPLE 32

REACTION SCHEMES, PART 8 CONT'D



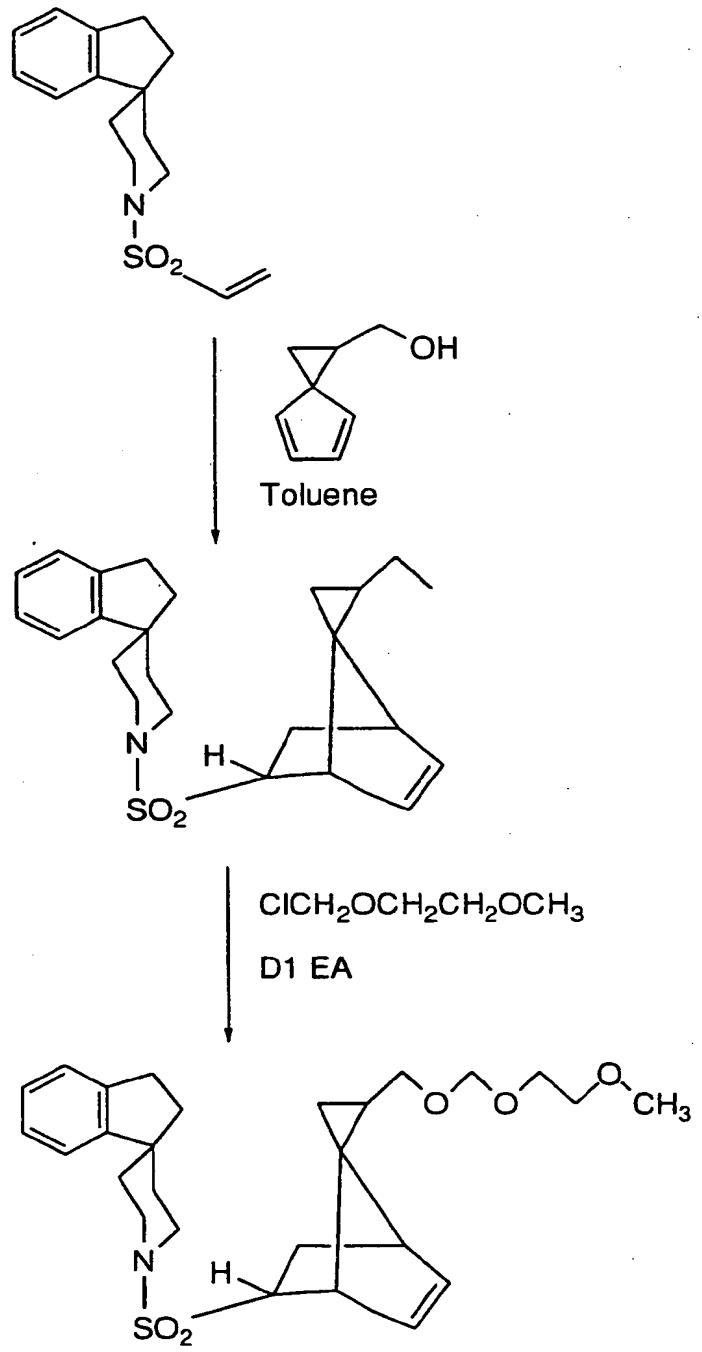

EXAMPLE 33

REACTION SCHEMES, PART 8 CONT'D



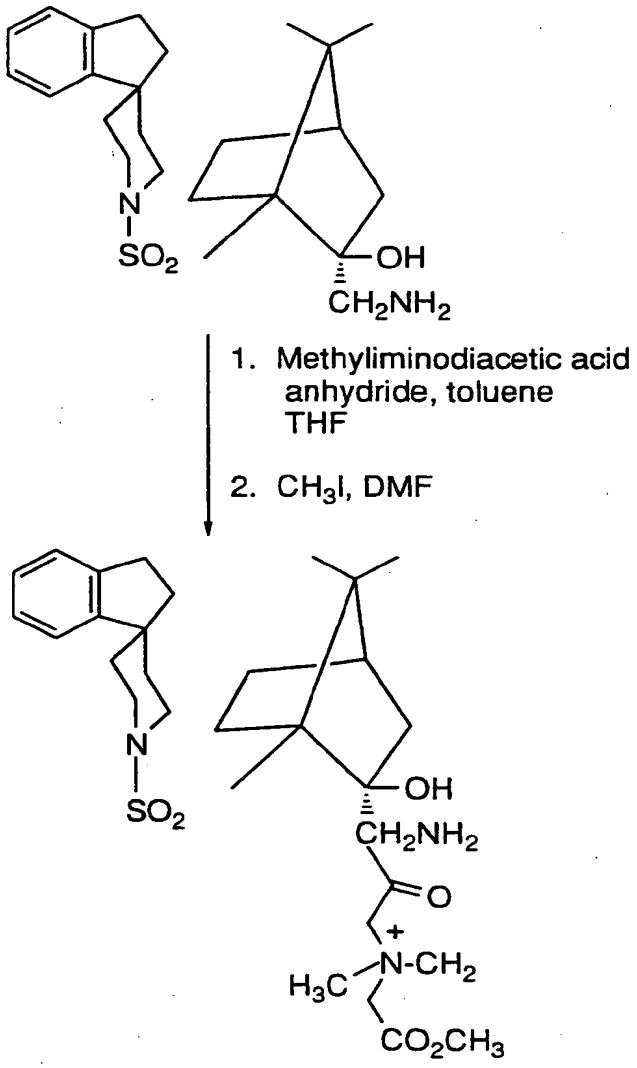

EXAMPLE 34

REACTION SCHEMES, PART 9



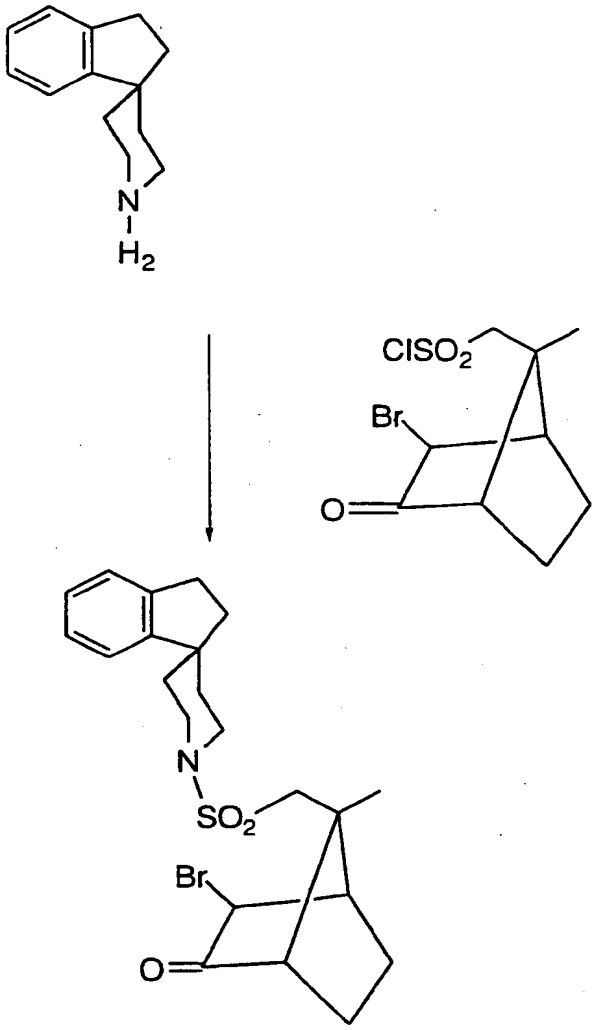

EXAMPLE 35

## REACTION SCHEMES, PART 10



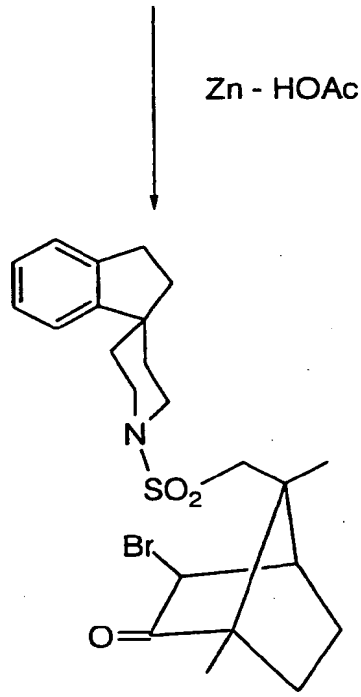

## EXAMPLE 36

REACTION SCHEMES, PART 11



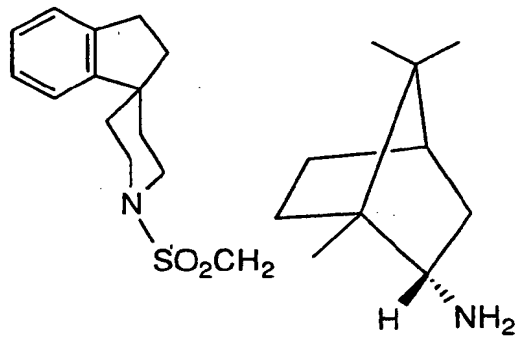

EXAMPLE 37

REACTION SCHEMES, PART 11 CONT'D




EXAMPLE 38

EXAMPLE A




Endo-(1S)-1'(((2-amino-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine)

Di-t-butyl dicarbonate (31g, 0.14 mole available from Aldrich) and bis(2-chloroethyl)amine hydrochloride (21.6g, 0.12 mole Aldrich) were combined in $CH_2Cl_2$ (250 ml) stirred at ambient temperature and treated with triethylamine (12.8 g, 0.127 mole) added dropwise over 15 minutes. After 1 hour, another 1.5 ml of triethylamine was added. After a total of 2.5 hours, the mixture was poured onto a silica gel column packed with $CH_2Cl_2$:hexane (1:1), and eluted with $CH_2Cl_2$. The combined product fractions were evaporated to dryness in vacuo to give N,N-bis(2-chloroethyl)-t-butyl-carbamate.

To a solution of indene (10.3 g, 89 mmole) in dry tetrahydrofuran (THF, 18 ml) cooled in an ice bath and maintained under a nitrogen blanket was added lithium bis(trimethylsilyl)amide (Aldrich, 177 ml of a 1.0M solution in THF; 177 mmole) over 15 minutes. The mixture was stirred in the cold for 30 minutes, then added over 15 minutes to a solution of N,N-bis(2-chloroethyl)-t-butylcarbamate (21.2 g, 88 mmole) stirred in an ice bath. The mixture was stirred for 2 hours in the cold and for 30 minutes at ambient temperature under nitrogen, then evaporated in vacuo to a foam. $CH_2Cl_2$ was added and the resulting mixture poured onto a silica gel column packed with 40% hexane in $CH_2Cl_2$. The column

was eluted with 40% hexane in $CH_2Cl_2$ followed by $CH_2Cl_2$, and the product fractions were evaporated to dryness in vacuo to provide 1'-(t-butyloxycarbonyl)-spiro(indene-1,4'-piperidine).

1'-(t-Butyloxycarbonyl)spiro(indene-1,4'-piperidine) (16 g, 56 mmole) in ethyl acetate (250 ml) was stirred in an ice bath and saturated with HCl(g) for 30 minutes. The mixture was evaporated to dryness. Ethyl acetate was added and removed in vacuo three times, and the residue was triturated with diethyl ether and filtered to provide spiro(1H-indene-1,4'-piperidine) hydrochloride. The free base was obtained by slurrying the hydrochloride in aqueous sodium bicarbonate solution and extracting with $CH_2Cl_2$. The organic layer was separated, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to provide spiro(1H-indene-1,4'piperidine.

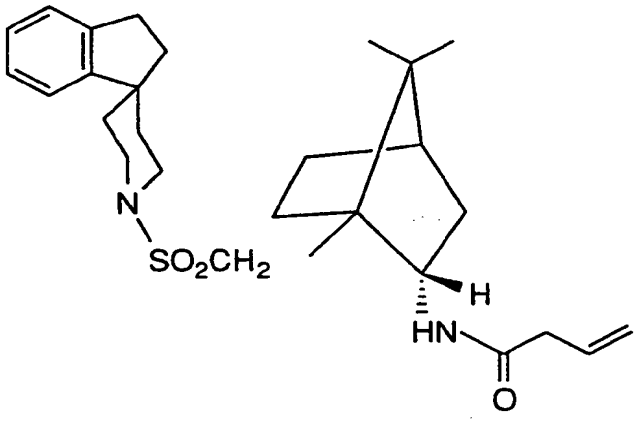
Spiro(1H-indene-1,4'piperidine) (308 mg, 1.66 mmol) and (+)-10-camphorsulfonyl chloride (418 mg, 1.66 mmol) were combined in $CH_2Cl_2$ and treated with triethylamine (0.23 ml). The mixture was stirred at ambient temperature for 15 minutes, then poured onto a silica gel column and eluted with 1:1 $CH_2Cl_2$:hexane. The product fractions were combined and evaporated to dryness in vacuo to provide (1S)-1'-(((7,7-dimethyl-2-oxobicicylo-(2.2.1) hept-1-yl)-methyl)sulfonyl)spiro-(1H-indene-1.4'-piperidine) as a solid which was recrystallized from petroleum ether and dried overnight in vacuo at ambient temperature.

(1S)-1'-(((7,7-dimethyl-2-oxobicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)spiro(1H-indene-1,4'-piperidine) (30 g, 0.075 mole) in pyridine (500 mL) was heated in an oil bath to 70°C (internal). Hydroxylamine hydrochloride (30 g) was added in three portions over ca. 20 minutes. After 2 hours, an additional 10 g of hydroxylamine hydrochloride was added (over 10 minutes). At 30, 40, and 50 minutes additional elapsed time, further 3 g lots of hydroxyl-amine hydrochloride were added. After another 30 minutes, the mixture was poured into water (2 L) and extracted 3 times with ethyl acetate (300 mL portions). The organic layers were combined, washed with 1N HCl (600 mL total), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. EtOH (abs; ca. 250 mL) was added to the resulting

thick syrup and the solution allowed to stand at ambient temperature overnight. The mixture was filtered and the filtrate boiled down to ca. 80 mL. After standing, the mixture was again filtered and boiled down to ca. 20 mL. After a third filtration, the filtered solids were combined to give (1S)-1'-(((7,7-dimethyl-2-oximinobicyclo(2.2.1)hept-1-yl)-methyl) sulfonyl)spiro(1H-indene-1,4'-piperidine) (28 g).

Freshly prepared, activated Raney Nickel catalyst (ca. 30 g) in water was allowed to settle and the water decanted. Abs. ethanol (300 mL) was added, and the mixture swirled and again allowed to settle. The solvent was decanted. Two more wash-decant cycles with 150 mL of ethanol were similarly carried out. (1S)-1'-(((7,7-dimethyl-2-oximinobicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine) (30 g) was stirred in a mixture of abs. ethanol (450 mL) and 2-methoxyethanol (900 mL), nitrogen was bubbled through the suspension/solution, and the Raney Nickel catalyst was added. The mixture was hydrogenated under 50 psi overnight. TLC (9:1 $CH_2Cl_2$MeOH, silica gel) showed the reaction to be complete. The catalyst was removed by filtration, and the filtrate evaporated to dryness in vacuo. The crude solid (27 g) was divided into 7 g batches, and each batch was dissolved in methylene chloride (ca. 200 mL) and flash chromatographed on silica (700 g in a 100 mm column, packed and eluted with 8% (v/v) methanol in methylene chloride), taking 200 mL fractions. The exo isomer of the title amine was obtained in fractions ca. 5-7, and the desired endo isomer in fractions ca. 8-16. TLC was on silica, eluted with 8% methanol-methylene chloride, phosphomolybdic acid stain. The combined product fractions were evaporated to dryness to provide the title compound (4.5 g from each 7 g lot, ca. 18 g total) as a colorless solid.

EXAMPLE 1

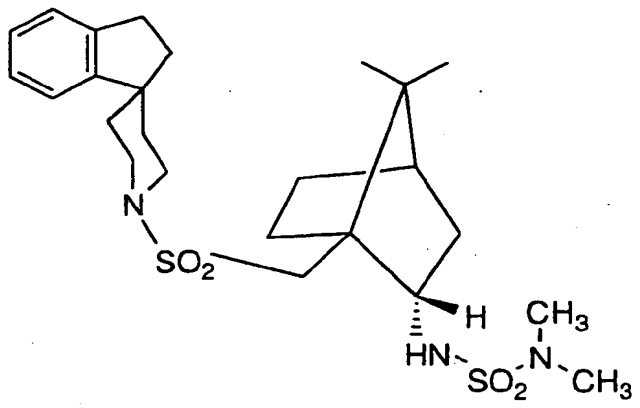



Endo-(1S)-1'-(((2-(but-3ene-1-ylamino)7,7-dimethyl-bicyclo(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-indan-1,4'-piperidine)

To a solution of endo-1S-1'-(((2-amino-7,7-dimethyl-bicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) (50 mg, 0.000125 m) in methylene chloride (3 ml) in an atmosphere of nitrogen was added crotonyl chloride (13.1 mg, 14 ml, 0.000125 M) via a syringe. After two minutes, triethylamine (50 ml) was added to make the solution basic (ph=9). After 1 hour, the reaction mixture was concentrated and the oil was chromatographed on a silica "flash" column using 40% ethyl acetate in hexane as solvent. Fractions 27-40 contained a fluorescent spot. These were concentrated and ether-hexane was added and concentrated to yield the title compound as a white foam.

NMR ($CDCl_3$) was consistent with structure.
HPLC: 210-97.181% 254-99.386%
Mass Spectra: Calculated, m/e=470.679; Found, m/e=471.3
Analysis calculated for $C_{27}H_{38}N_2O_3S$
C, 68.90; H, 8.14; N, 5.95
Found: C, 68.99; H, 8.19; N, 5.7

EXAMPLE 2

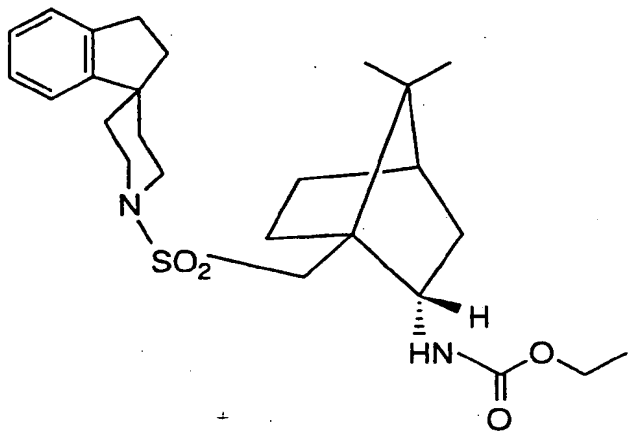


Endo-(1S)-1'-(((2-(dimethylaminosulfonylamino)-7,7-dimethyl-bicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M) in methylene chloride (3 ml). Dimethylaminosulfonyl chloride (17.9 mg, 0.000125 M) was added, and after two minutes, triethylamine (50 ml) was added. After one hour, the reaction mixture was concentrated under reduced pressure (20 mm). A silica "flash" column using methylene chloride(9)-methanol(1) as solvents was used to purify the title compound as a tan solid after adding and concentrating with hexane.

NMR ($CDCl_3$) was consistent with structure.
HPLC: 210-96.47% 254-100%
Mass Spectra: Calculated, 509.736; Found, 510.3
Analysis calculated for $C_{25}H_{39}N_3O_4S_2$
C, 59.51; H, 7.93; N, 8.04
Found: C, 59.58; H, 7.71; N, 7.87

EXAMPLE 3

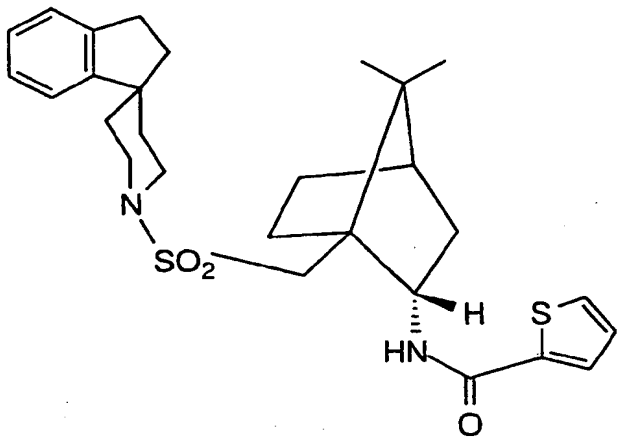


Endo-(1S)-1'-(((2-(ethoxycarbonylamino)-7,7-dimethyl-bicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M) in methylene chloride (3 ml). Ethyl chloroformate (13.6 mg, 12 ml, 0.000125 M) was added via syringe. After two minutes, triethylamine (50 ml) was added to make the solution basic (pH=9). After 30 minutes, the reaction mixture was concentrated under reduced pressure (20 mm). The oil was chromatographed on a silica "flash" column with 40% ethyl acetate in hexane as eluent. Fractions 12-20 contained the product. These fractions were concentrated under reduced pressure (20 mm). Hexane-ether was added to the oil and removed under reduced pressure to yield 17 mg of the title compound as a white powder.
NMR ($CDCl_3$) was consistent with structure.

HPLC 210-99.817% 254-100%
Mass Spectra: Calculated 474.668, Found 475.3
Analysis calculated for $C_{26}H_{38}N_2O_4S$
C, 65.79; H, 8.07; N, 5.90
Found: C, 66.05; H, 8.22; N, 5.72

EXAMPLE 4

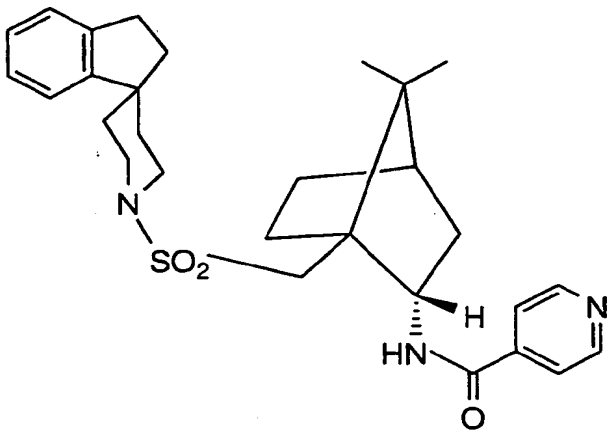



Endo-(1S)-1'-(((2-(2-thiophenecarbonylamino)-7,7-dimethylbicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 m) in methylene chloride (3 ml). The 2-thiophene carbonyl chloride (18 mg, 13.4 ml, 0.000125 m) was added via syringe. Triethylamine (50 ml) was added to make the mixture basic. The reaction mixture was concentrated to oil and chromatographed using a silica "flash" column with 40% ethyl acetate in hexane as eluent. Fractions 12-20 contained the product. Fractions 11-18 contained the desired product and these were concentrated to an oil. Ether-hexane was added and removed to yield 27 mg of the title compound as a white amorphous powder.

HPLC 210-98.873% 254-97/931%
Mass Spectra: Calculated, 512.738; Found, 513.3
Analysis calculated for C28H36N2O3S2 0.72 hexane
C, 63.97; H, 7.11; N, 5.33
Found: C, 63.59; H, 6.78; N, 5.08

EXAMPLE 5

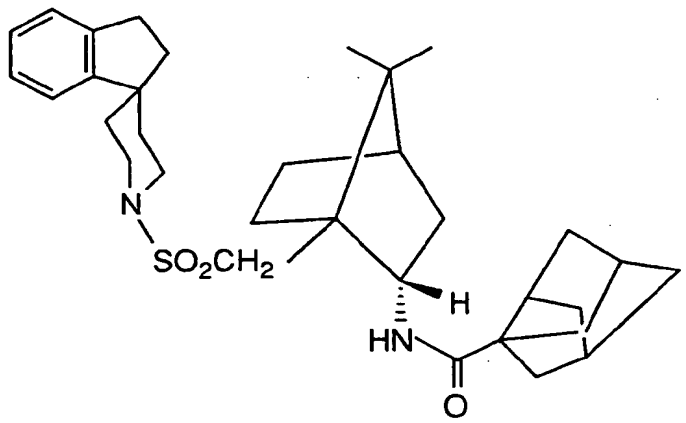



Endo-(1S)-1'-(((2-(isonicotinylamino)-7,7-dimethyl-bicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 m) in methylene chloride (3 ml). The isonicotinoyl chloride dihydrochloride (22.38 mg, 0.000125 m) was added. After 2 minutes, triethylamine (50 ml) was added so the pH equaled 9. The solvent was removed under reduced pressure and the product was purified by a "flash" silica column using methylene chloride (9)-methanol (1) as solvents. The product was contained in fractions 6-10 which were concentrated. The oil was treated with hexane-ether which was removed under reduced pressure. This gave 18 mg of the title compound as a white foam.

NMR ($CDCl_3$) was consistent with structure.
HPLC 210-95.84% 254-98.04%
Mass Spectra: Calculated, 507.7; Found, 508.3
Analysis calculated for $C_{29}H_{37}N_3O_3S$
C, 68.61; H, 7.35; N, 8.28
Found: C, 68.46; H, 6.99; N, 7.90

EXAMPLE 6




Endo-(1S)-1'-(((2-(noradamantyl-1-carbonylamino)-7,7-dimethyl-bicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)

Step 1: Noradamantyl-1-carbonyl chloride

To a solution of noradamantylcarboxylate (20.8 mg, 0.000125 M) in methylene chloride (4 ml) in a round bottom flask (50 ml) under an atmosphere of nitrogen at 0°C was added oxalyl chloride (120 ml) via syringe. Dimethylformamide (7 ml) was added and the solution was stirred at 0°C for 15 minutes. The reaction mixture was allowed to warm to room temperature and stir for 45 minutes. The solvent was removed under reduced pressure (20 mm). Twice additional methylene chloride was added and removed under reduced pressure. The acid chloride of the title compound was kept under high vacuum (0.05 mm) for one hour before using in the next step.

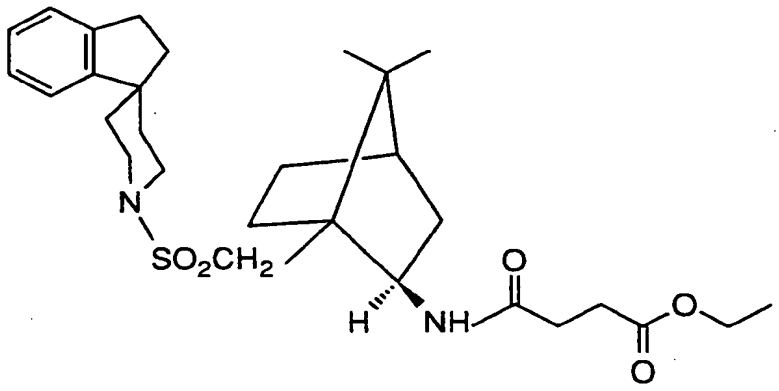
Step 2: Endo-(1S)-1'-(((2-(noradamantyl-1-carbonylamino)-7, 7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)sulfonyl)-spiro(1H-indan-1,4'-piperidine)

Adamantyl-1-carbonyl chloride was dissolved in methylene chloride (4 ml) and endo-1S-1'-(((2- amino-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) (50 mg, 0.000125 m) was added. After two minutes, triethylamine (100 ml) was

introduced via syringe. The solvent was removed under reduced pressure and the oil was chromatographed on silica with 40% ethyl acetate in hexane as elutant. The product fractions were collected and concentrated to an oil, which became an amorphous white solid upon addition and removal of ether-hexane. This gave 10 mg of the title compound.

NMR (CDCl3) was consistent with structure.
HPLC 210-98.427% 254-100%
Mass Spectra: Calculated, m/e 550.81; Found, m/e 551.3
Analysis calculated for $C_{33}H_{46}N_2O_3S$
C, 71.96; H, 8.42; N, 5.09
Found: C, 71.57; H, 8.71; N, 4.77

EXAMPLE 7



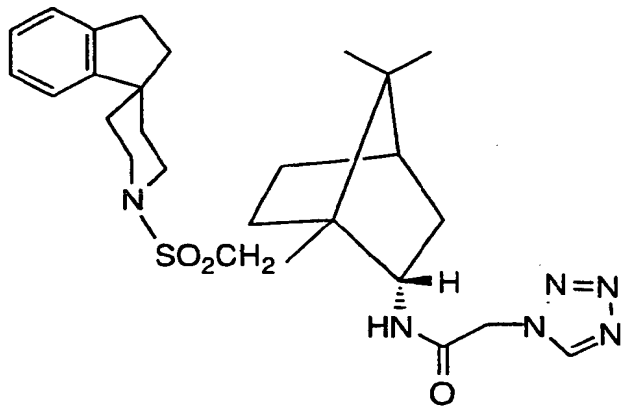

Exo-(1S)-1'-(((2-(ethyl succinoylamino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine)

To a solution of exo-(1S)-1'-(((2-(amino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) (50 mg, 0.000125 M) in methylene chloride (3 ml) under a blanket of nitrogen was added ethyl succinoyl chloride (20.6 mg, 0.000125 M). After two minutes, triethylamine (50 ml) was added with a syringe. The pH of the solution was 9. After 15 minutes, a new spot was observed on the tlc (silica-40% ethyl acetate in hexane). The reaction mixture was concentrated and the oil was chromatographed on

a silica "flash" column with 40% ethyl acetate as solvent. Fractions 24-48 contained the product. These fractions were collected and concentrated. Ether-hexane was added and removed to yield 21.3 mg of the title compound as a white powder.

NMR ($CDCl_3$) was consistent with structure.
HPLC 210-99.190% 254-96.914%
Mass Spectra: Calculated m/e, 530.732; Found m/e, 531.5
Analysis calculated for $C_{29}H_{42}N_2O_5S$ " 0.25 $H_2O$
C, 65.08; H, 8.00; N, 5.23
Found: C, 65.16; H, 8.03; N, 5.09

## EXAMPLE 8



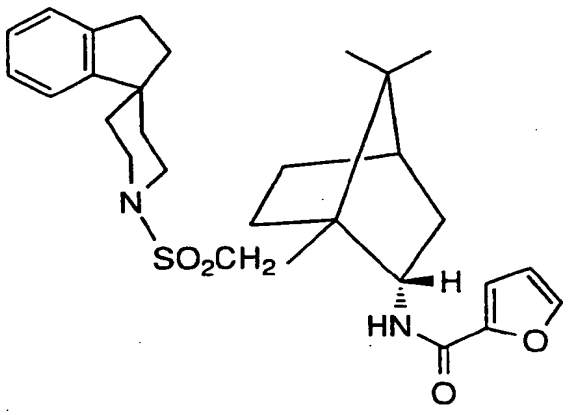

Endo-(1S)-1'-(((2-(tetrazole-1-acetylamino)-7,7-dimethylbicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M), tetrazole-1-acetic acid (16 mg, 0.000125 M), and benzotriazol-1-yloxytris(dimethylamino)phosphonium-hexafluorophosphate (Sequalog) (55 mg, 0.000125 M) in acetonitrile (3 ml). Diisopropylethylamine (50 ml) was added to make the solution basic. After tlc (silica-methylene chloride(9)-methanol(1)) showed a new spot, the reaction was concentrated to an oil. The oil was dissolved in methylene chloride-

ether (1:3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and brine. After drying with sodium sulfate, the solution was filtered and concentrated to oil, which was chromatographed on a silica "flash" column with 10% methanol in methylene chloride. Fractions 5-10 contained the product and were collected and concentrated. Ether-hexane was added and removed to yield the title compound as a white powder.

NMR ($CDCl_3$) was consistent with structure.
HPLC: 210-98% 254-100%
Mass Spectra: Calculated, 513.679; Found, 513.3
Analysis calculated for $C_{26}H_{36}N_6O_3S$ " 0.25 $H_2O$
C, 60.37; H, 7.11; N, 16.25
Found: C, 60.28; H, 6.96; N, 16.18

EXAMPLE 9



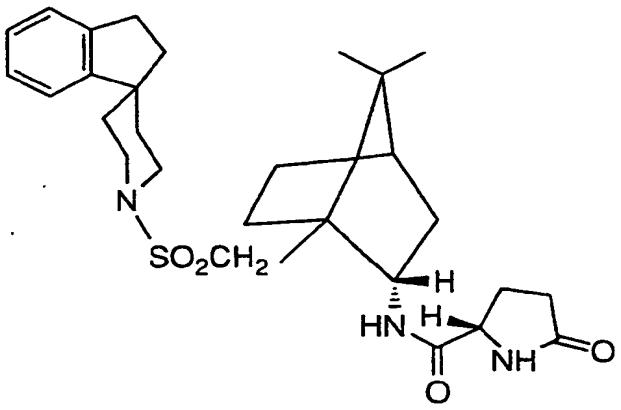

Endo-(1S)-1'-(((2-(2-furoylamino)-7,7-dimethylbicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M) in methylene chloride (3 ml) and 2-furoyl chloride (16.3 mg, 0.000125 M) was added. After two minutes, triethylamine (150 ml) was added so the pH equaled 9. The solvent was removed under pressure and the

product was purified by a silica "flash" column using 40% ethyl acetate in hexane as solvents. The product was contained in fractions 6-10 which were concentrated. The oil was treated with hexane-ether which was removed under reduced pressure.

NMR ($CDCl_3$) was consistent with structure.
HPLC: 210-99.341% 254-99.576%
Mass Spectra: Calculated, 496.674; Found, 497.3
Analysis calculated for $C_{28}H_{36}N_2O_4S$
C, 67.71; H, 7.31; N, 5.64
Found: C, 67.41; H, 7.39; N, 5.46

EXAMPLE 10



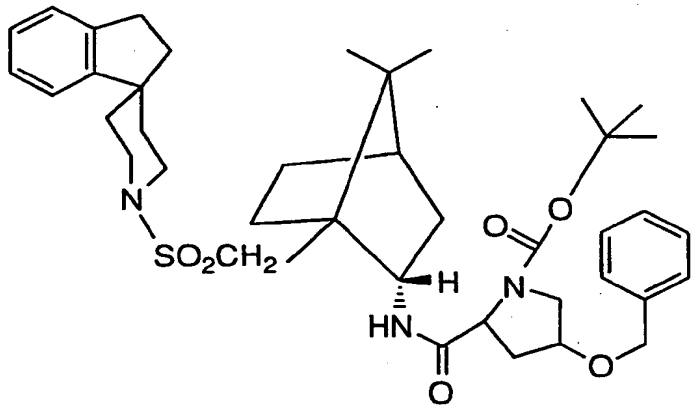

Endo-(1S)-1'-(((2-(S-(1)-2-oxo-pyrrolidin-5-yl-carbonyl)amino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M), S-(1)-2-oxo-pyrrolidine-5-carboxylic acid (16.1 mg, 0.000125 M), and benzotriazol-1-yloxytris(dimethyl-amino)phosphonium-hexafluoro-phosphate (Sequalog) (55 mg, 0.000125 M) in acetonitrile (3 ml). Diisopropyl-ethylamine (50 ml) was added to make the solution basic. After tlc(silica-methylene chloride(9)-methanol(1)) showed a new spot,

the reaction was concentrated to an oil. The oil was dissolved in methylene chloride-ether(1:3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and brine. After drying with sodium sulfate, the solution was filtered and concentrated to an oil. Ether-hexane was added and removed under reduced pressure to give the title compound as a white solid.

NMR ($CDCl_3$) was consistent with structure.
HPLC: 210-93.102% 254-92.292%
Mass Spectra: Calculated, 513.705; Found, 514.3

EXAMPLE 11



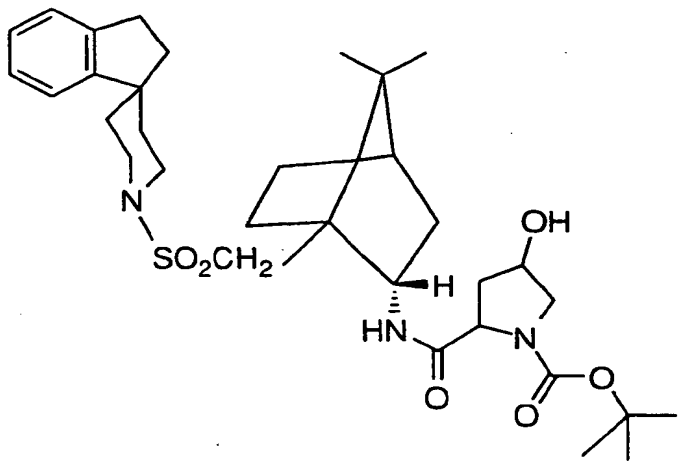

Endo-(1S)-1'-(((2-(L-N-(tert.-butoxycarbonyl)-4-benzyl-oxy-prolinoylamino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M), L-N(tert.-butoxycarbonyl)-4-benzyloxy-proline (40.2 mg, 0.000125 M), and benzotriazol-1-yloxytris(dimethylamino)phosphonium-hexafluorophosphate sequalog (55 mg, 0.000125 M) in acetonitrile (3 ml). Diisopropylethylamine (50 ml) was added to make the solution basic. After tlc(silica-methylene chloride(9)-methanol(1)) showed a new spot, the reaction was concentrated to an oil. The oil was dissolved

in methylene chloride-ether(1:3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and brine. After drying with sodium sulfate, the solution was filtered and concentrated to an oil which was purified by "flash" silica chromatography with 40% ethyl acetate in hexane as solvent. Fractions 15-24 contained the product and they were collected and concentrated. Ether-hexane treatment provided a white solid which was the title compound. A 10 mg sample was used for characterization and testing with the remainder being used in subsequent steps.

NMR ($CDCl_3$) was consistent with structure.
HPLC: 210-99.003% 254-100%
Mass Spectra: Cal'd, 705.965; Found, 706
Analysis calculated for $C_{40}H_{55}N_3O_6S$ " 0.25 $H_2O$
C, 67.62; H, 7.87; N, 5.91
Found: C, 67.56; H, 8.11; N, 5.59

EXAMPLE 12




Endo-(1S)-1'-(((2-(L-N(tert.-butoxycarbonyl)-4-hydroxy-prolinoylamino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)methyl-sulfonyl)spiro(1H-indan-1,4-piperidine)

A mixture of Endo-(1S)-1'-(((2-(L-N(tert.-butoxy-carbonyl)-4-benzyloxy-prolinoylamino)-7,7-dimethyl)bicyclo(2.2.1)-

hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine), ethanol (5 ml), and $Pd(OH)_2$ (60 mg) was hydrogenated on the Parr apparatus at 50 psi for 18 hours. The catalyst was removed by filtration and the solvent was removed under reduced pressure to yield the title compound as a white solid.

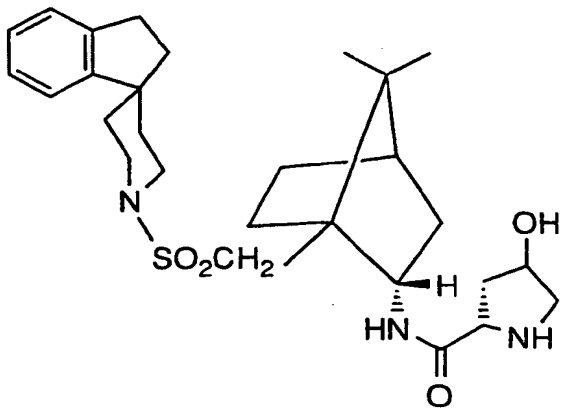
NMR ($CDCl_3$) was consistent with structure.

HPLC: 210-93.5% 254-(7.381%

Mass Spectra: Calculated, 615.840; Found, 616

Analysis calculated for $C_{33}H_{49}N_3O_6S$ " 1.5 $H_2O$
C, 61.65; H, 8.15; N, 6.53
Found: C, 61.46; H, 7.88; N, 6.90

EXAMPLE 13



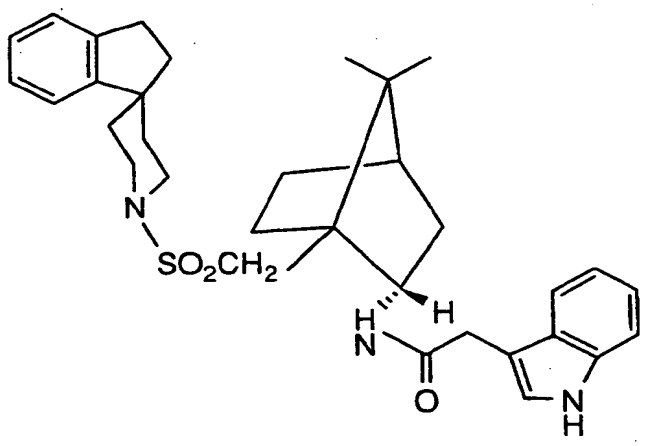

Endo-(1S)-1'-(((2-(L-4-hydroxyprolinoylamino)-7,7-dimethyl-bicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)hydrochloride

A mixture of Endo-(1S)-1'-(((2-(L-N(tert.-butoxy-carbonyl)-4-hydroxyprolinoylamino)-7,7-dimethyl)bicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine), was dissolved in ethyl acetate (5 ml) and cooled to -5°C. This was placed under a nitrogen atmosphere and hydrogen chloride gas was bubbled in for 10 minutes. The solvent was removed under reduced pressure. Ether was

added and removed under reduced pressure to give 15.48 mg of the title compound as a white solid.

NMR ($CDCl_3$) was consistent with structure.
HPLC: 210-93.50% 254-93.812%
Mass Spectra: Calculated, 515.721 (free base); Found, 516.4
Analysis calculated for $C_{28}H_{41}N_3O_4S$ HCl 0.25 $H_2O$
C, 60.41; H, 7.69; N, 7.54
Found: C, 60.08; H, 7.73; N, 7.35

EXAMPLE 14




Endo-(1S)-1'-(((2-(3-indolylacetylamino)7,7-dimethyl-bicyclo-(2.2.1)-hept-1-yl)methyl-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M), 3-indolyl acetic acid (21.9 mg, 0.000125 M), and benzotriazol-1-yloxytris(dimethylamino)phosphonium-hexafluorophosphate (Sequalog) (55 mg, 0.000125 M)in acetonitrile (3 ml). Diisopropylethylamine (50 ml) was added to make the solution basic. After tlc(silica-methylene chloride(9)-methanol(1)) showed a new spot, the reaction was concentrated to an oil. The oil was dissolved in methylene chloride-ether (1:3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and brine. After

drying with sodium sulfate, the solution was filtered and concentrated to an oil which was purified by "flash" silica chromatography with 10% methanol in methylene chloride as solvent. Fractions 12-19 contained the product and they were collected and concentrated. Ether-hexane treatment provided a white solid which was the title compound.

MR ($CDCl_3$) was consistent with structure.

HPLC: 210-99.829% 254-92.699%

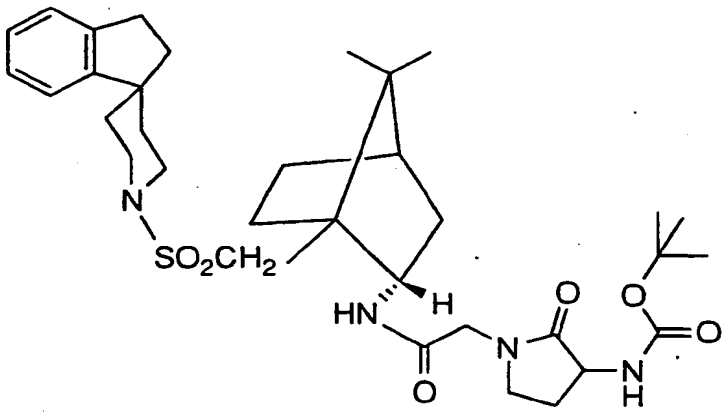
Mass Spectra: Calculated, 559.777; Found, 560.3

Analysis calculated for $C_{33}H_{41}N_3O_3S$ " 0.5 $H_2O$

C, 69.69; H, 7.44; N, 7.51

Found: C, 69.70; H, 7.57; N, 7.20

EXAMPLE 15




Endo-(1S)-1'-(((2-(S-3-(tert.-butoxycarbonyl)amino)-2-oxo-1-pyrrolidineacetylamino)7,7-dimethylbicyclo-(2.2.1)hept-1-yl)-methylsulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M), S-3-((tert.-butoxycarbonyl)amino)-2-oxo-1-pyrrolidine acetic acid (32.2 mg, 0.000125 M), and benzotriazol-1-yloxytris (dimethylamino)-phosphoniumhexafluoro-phosphate (Sequalog) (55 mg, 0.000125 M) in acetonitrile (3 ml). Diisopropylethylamine (50 ml) was added to make

the solution basic. After tlc(silica-methylene chloride(9)-methanol(1)) showed a new spot, the reaction was concentrated to an oil. The oil was dissolved in methylene chloride-ether(1:3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and brine. After drying with sodium sulfate, the solution was filtered and concentrated to an oil which was purified by "flash" silica chromatography with 10% methanol in methylene chloride as solvent. Fractions 15-28 contained the product and they were collected and concentrated. Ether-hexane treatment provided a white solid which was the title compound.

NMR ($CDCl_3$) was consistent with structure.

HPLC: 210-94.005% 254-96.33%

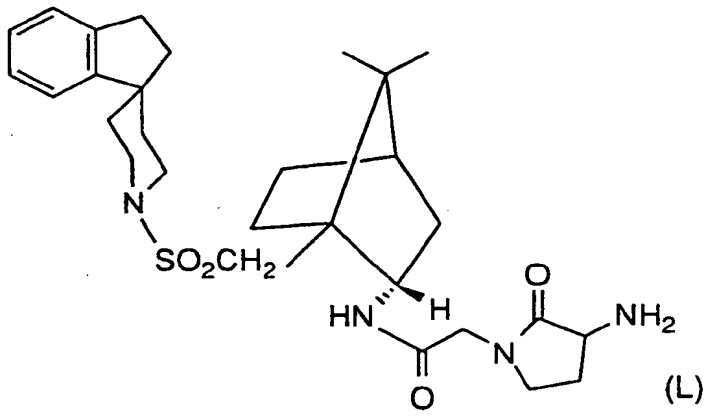
Mass Spectra: Calculated m/e, 642.859; Found m/e, 643.4

Analysis calculated for $C_{34}H_{50}N_4O_6S$ " 0.1 hexane

C, 63.79; H, 7.95; N, 8.59

Found: C, 63.66; H, 8.32; N, 8.29

## EXAMPLE 16




(L)

Endo-(1S)-1'-(((2-(S-3-amino)-2-oxo-1-pyrrolidine-acetylamino)7, 7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)hydrochloride

Endo-1S-1'-(((2-(S-3-(tert.-butoxycarbonyl)amino)-2-oxo-1-pyrrolidineacetylamino-)-7,7-dimethyl-bicyclo(2.2.1.)hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) was dissolved in ethyl acetate (5 ml) and cooled to -5°C. This was placed under a nitrogen atmosphere and hydrogen chloride gas was bubbled in for 10 minutes. The solvent was removed under reduced pressure. Ether was added and removed under reduced pressure to give 23.7 mg of the title compound as a white solid.

NMR ($CDCl_3$) was consistent with structure.

HPLC: 210-96.562% 254-95.493%

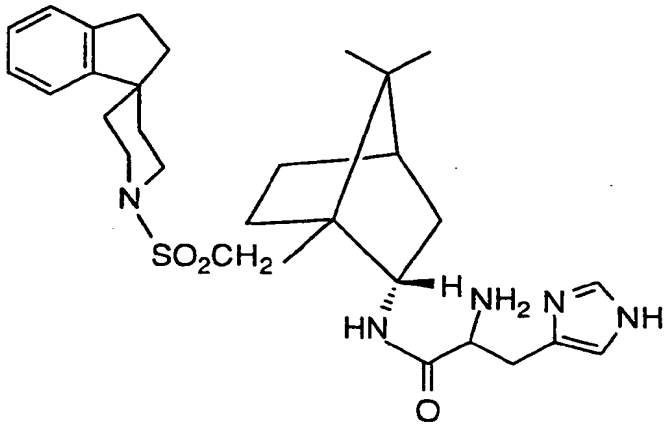
Mass Spectra: Calculated for free base m/e, 542; Found m/e, 543.3

Analysis calculated for $C_{29}H_{42}N_4O_4S$ " $H_2O$ " HCl

C, 58.32; H, 7.59; N, 9.38

Found: C, 58.14; H, 7.97; N, 9.21

## EXAMPLE 17




Step 1: Endo-(1S)-1'-(((2-(L-N-tertbutoxycarbonyl-histidinoyl-amino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven dried flask (50 ml) under nitrogen were dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) (50 mg, 0.000125 M), L-N-tert, butoxycarbonyl histidine (29.9 mg, 0.000125 M), and benzotriazol-1-yloxytris(dimethylamino)phosphonium-hexafluoro-phosphate (Sequalog) (55 mg, 0.000125 M) in acetonitrile (3 ml). Diisopropylethylamine (50 ml) was added to make the solution basic. After tlc(silica-methylene chloride(9)-methanol(1)) showed a new spot, the reaction was concentrated to an oil. The oil was dissolved in methylene chloride-ether (1:3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and brine. After drying with sodium sulfate, the solution was filtered and concentrated to an oil, which was purified by "flash" silica chromatography with 10% methanol in methylene chloride as solvent. Fractions 15-28 contained the product and they were collected and concentrated. Ether-hexane treatment provided a white solid which as the title compound.

NMR ($CD_3OD$) was consistent with structure.
HPLC: 210-97.822% 254-100%
Mass Spectra: Calculated m/e, 639.859; Found m/e, 640.3

Step 2: Endo-(1S)-1'-(((2-(L-N-histidinoylamino)-7,7-dimethyl-bicyclo(2.2.1)-hept-1-yl)-methyl-sulfonyl)spiro(1H-indan-1,4-piperidine)

Endo-1S-1'-(((2-(L-N-tert.butoxycarbonyl-histidinoyl-amino)-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)-spiro(1H-indan-1,4'-piperidine) (50 mg, 0.000125 M) was dissolved in ethyl acetate (5 ml) and cooled to -5°C. This was placed under a nitrogen atmosphere and hydrogen chloride gas was bubbled in for 10 minutes. The solvent was removed under reduced pressure. Ether was added and removed under reduced pressure to give 27.5 mg of the title compound as a white solid.

NMR ($CD_3OD$) was consistent with structure.

HPLC: 210-98.652% 254-100%

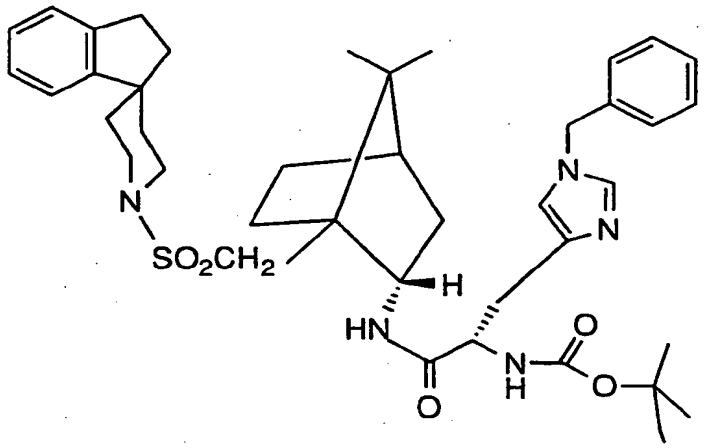
Mass Spectra: Calculated for free base m/e, 539.7; Found m/e, 540.3

Analysis calculated for $C_{29}H_{41}N_5O_3S\ 2HCl\ 2H_2O$

C, 53.69; H, 7.30; N, 10.79

Found: C, 53.58; H, 7.45; N, 11.00

EXAMPLE 18




Endo-(1S)-1'-(((2-(D-N-(tert.butoxycarbonyl)-im-benzylhistidino-ylamino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)sulfonyl)-spiro(1H-indan-1,4'-piperidine)

In an oven-dried flask (50 ml) under nitrogen were dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) (50 mg, 0.000125 M), D-N-tert. butoxycarbonylim-benzyl-histidine (43 mg, 0.000125 M), and benzotriazol-1-yloxytris(dimethylamino)phosphoniumhexafluoro-phosphate (Sequalog) (55 mg, 0.000125 M) in acetonitrile (3 ml). Diisopropyl-ethylamine (50 ml) was added to make the solution basic. After tlc(silica-methylene chloride(9)-methanol(1)) showed a new spot, the reaction was concentrated to an oil. The oil was dissolved in methylene chloride-ether (1:3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and brine. After drying with sodium sulfate, the solution was filtered and

concentrated. Ether-hexane provided a white solid which was the title compound.

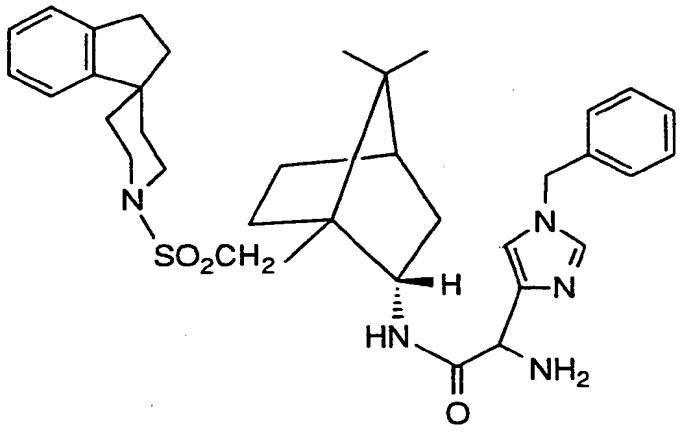
NMR ($CDCl_3$) was consistent with structure.

HPLC: 210-99.551%

Mass Spectra: Calculated, m/e 730.062; Found, m/e 730.6

Analysis calculated for $C_{41}H_{55}N_5O_5S$: 0.65 $H_2O$ 0.4 hexane
C, 67.15; H, 8.04; N, 9.02
Found: C, 67.18; H, 7.73; N, 9.02

EXAMPLE 19



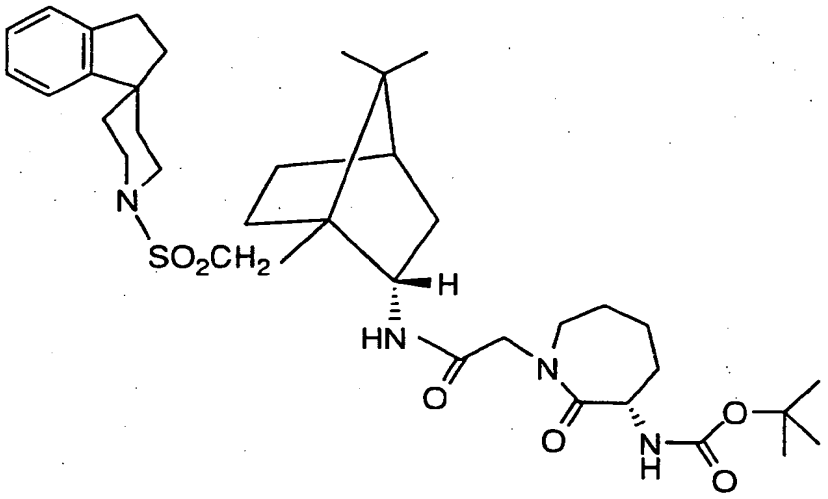

Endo-(1S)-1'-(((2-(D-im-benzylhistidinoylamino)-7,7-dimethyl-bicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4-piperidine)-hydrochloride

Endo-(1S)-1'-(((2-(D-N-(tert.butoxycarbonyl)-im-benzylhistidinoylamino)-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) was dissolved in ethyl acetate (5 ml) and cooled to -5°C. This was placed under a nitrogen atmosphere and hydrogen chloride gas was bubbled in for 10 minutes. The solvent was removed under reduced pressure. Ether was added and removed under reduced pressure to give the title compound as a white solid.

NMR ($CDCl_3$) was consistent with structure.

HPLC: 210-100%
Mass Spectra: Calculated m/e, 629.879; Found m/e, 630
Analysis calculated for $C_{36}H_{47}N_5O_3S$ HCl 0.1 ethyl acetate 1.4 $H_2O$
C, 59.33; H, 7.20; N, 9.51
Found: C, 59.36; H, 7.03; N, 9.50

EXAMPLE 20



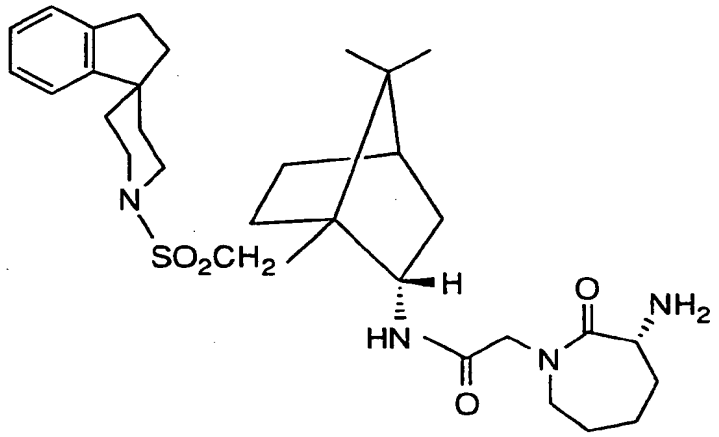

Endo-(1S)-1'-(((2-(S-3-tert.butoxycarbonylamino-2-oxo-1-azepineacetylamino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl-sulfonyl)spiro(1H-indan-1,4-piperidine)

In an oven-dried flask (50 ml) under nitrogen was dissolved endo-1S-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine)(50 mg, 0.000125 M), S-3-tert.butoxycarbonylamino-2-oxo-1-azepine acetic acid (32.8 mg), and benzotriazol-1-yloxytris (dimethylamino)phosphonium-hexafluoro-phosphate sequalog (55 mg, 0.000125 M) in acetonitrile (3 ml). Diisopropylethylamine (50 ml) was added to make the solution basic. After tlc(silica-methylene chloride(9)-methanol(1)) showed a new spot, the reaction was concentrated to an oil. The oil was dissolved in methylene chloride-ether(1.3) and the solution was washed with water, sodium bicarbonate (sat., aqueous), water, 10% potassium bisulfate, and

brine. After drying with sodium sulfate, the solution was filtered and concentrated to an oil, which was purified by "flash" silica chromatography with 10% methanol in methylene chloride as solvent. The fractions which contained the product were collected and concentrated. Ether-hexane treatment provided a white solid which was the title compound. A 10 mg sample was saved for characterization and testing.

NMR ($CDCl_3$) was consistent with structure.
HPLC 210-100%
Mass Spectra calculated m/e 670.918 found m/e 671
Analysis calculated for $C_{36}H_{54}N_4O_6S$
C, 64.44; H, 8.11; N, 8.35
Found: C, 64.12; H, 8.23; N, 8.03

EXAMPLE 21




Endo-(1S)-1'-(((2-(S-3-amino-2-oxo-1-azepine acetyl-amino)-7,7-dimethylbicyclo(2.2.1)-hept-1-yl-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) hydrochloride

Endo(1S)-1'-(((2-(S-3-tert-butoxycarbonyl-amino-2-oxo-1-azepine acetylamino)-7,7-dimethylbicylo-(2.2.1.)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine) was dissolved in ethyl acetate (5 ml) and cooled to 5°C. This was placed under a nitrogen atmosphere and hydrogen chloride gas was bubbled in for 10 minutes. The solvent

was removed under reduced pressure. Ether was added and removed under reduced pressure to give the title compound as a white solid.

NMR($DCDl_3$) was consistent with structure.

HPLC 210-100%

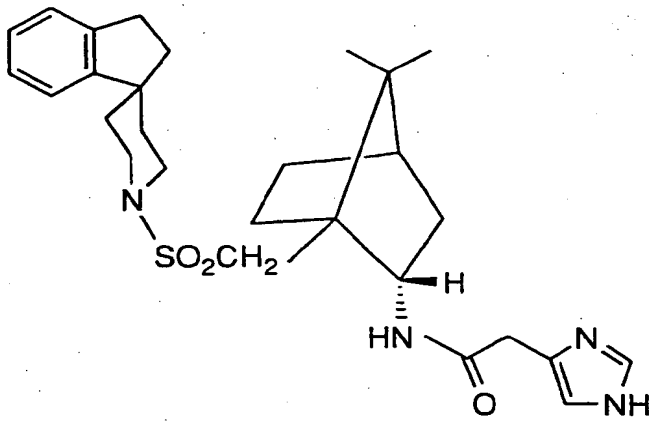
Mass Spectra: Calculated m/e, 570.802; Found m/e, 571

Analysis calculated for $C_{31}H_{46}N_4O_4S$ " HCl 1.10 $H_2O$ " 0.40 ethyl acetate

C, 59.11; H, 7.97; N, 8.46

Found: C, 59.09; H, 8.00; N, 8.45

EXAMPLE 22




Endo-(1S)-1'-(((2-(4-imidazoleacetylamino)-7,7-dimethylbicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indane-1,4'-piperidine)-hydrocloride

N,N-bis(2-chloroethyl)-t-butylcarbamate

Di-t-butyldicarbonate (62 g, 0.28 mole, available from Aldrich) and bis(2-chloroethyl)amine hydrochloride (55 g, 0.21 mole ,available from Aldrich) were stirred together in methylene chloride (400 mL). Triethylamine (42 mL, 0.3 mole) was added dropwise but briskly to the stirred suspension. After 10 minutes, additional triethylamine (ca. 5-6 mL) was added to adjust the pH of the mixture (as determined by spotting a sample on E. Merck pH 5-10 colorpHast sticks,

moistened with water) to 9-9.5. The mixture was stirred for 1 hour at ambient temperature, then filtered. The filtrate was divided in half, and each half (ca. 300 mL) was flash chromatographed on a separate 15", 2"diameter silica column packed with 3:2 (v:v) methylene chloride:hexane and eluted with 9:1 methylene chloride:hexane. 100 mL fractions were taken, and the product was obtained in fractions ca. 6-12. Assay was by TLC on silica gel plates, eluted with methylene chloride and visualized with phosphomolybdic acid stain ($R_f$ ca. 0.75). Evaporation of the combined product fractions from both columns in vacuo provided the title compound (70 g) as a colorless oil. The oil was twice dissolved in dry THF and evaporated in vacuo to remove methylene chloride.

1'-(t-Butyloxycarbonyl)spiro(1H-indene-1,4'-piperidine)

To a solution of indene (36.2 g, 310 mmole) in dry tetrahydrofuran (THF, 40 mL) cooled in an ice bath and maintained under a nitrogen blanket was added (dropped funnel) lithium bis(trimethylsilyl)-amide (620 mL of a 1.0 M solution in THF; 620 mmole, available from Aldrich) over 30 minutes. The mixture was stirred in the cold for 30 minutes, then transferred by cannula over 20 minutes to a solution of N,N-bis(2-chloroethyl)-t-butylcarbamate (70 g, 290 mmole) in THF (40 mL), stirred in an ice bath. The mixture was stirred for 2 hours in the cold and for 30 minutes at ambient temperature under nitrogen, then evaporated in vacuo to a foam. $CH_2Cl_2$ (400 mL) was added and the resulting mixture divided in half. Each half was poured onto a silica gel column (15", 2" id) packed and eluted with 1:1 hexane:$CH_2Cl_2$ (2 L) followed by 1:4 hexane: $CH_2Cl_2$. The product fractions (fractions 3-9 of 200 mL fractions) were evaporated to dryness in vacuo to provide 1'-(t-butyloxycarbonyl)spiro (indene-1,4'piperidine), 90 g total, as a crude yellow solid. The solid was taken up in boiling hexane (400 mL), cooled, and the crystallized solid filtered. The filtrate was repeatedly boiled down to 1/2 its volume, cooled and filtered to obtain successive crops, providing a total

of 54 g of pure product. The residue was rechromatographed to provide another 6.7 g (60.7 g total).

Spiro(1H-indene-1,4'-piperidine) hydrochloride

1'-(t-Butyloxycarbonyl)spiro(indene-1,4'-piperidine) (60.7 g) in ethyl acetate (700 mL) was stirred in an ice bath and saturated with HCl (g) for 30 minutes, keeping the internal temperature $\leq$ 12°C. The mixture was stirred in the cold an additional 30 minutes, then evaporated to dryness. Ethyl acetate was added and removed in vacuo three times, and the residue was triturated with diethyl ether and filtered to provide spiro(1H-indene-1,4'-piperidine) hydrochloride.

(1S)-1'-(((7,7-dimethyl-2-oxobicyclo(2.2.1)hept-1-)methyl)-sulfonyl)-spiro(1H-indene-1,4'-piperidine)

Spiro(1H-indene-1,4'piperidine) hydrochloride (45.4 g, 0.2 mole) and (+)-10-camphorsulfonyl chloride (62.5 g, 0.25 mole, available from Aldrich) were combined in $CH_2Cl_2$ (700 mL) and treated with triethylamine (68.5 mL, 0.5 mole). Additional triethylamine was added as needed to adjust the pH of the mixture to 9-9.5 (moistened E. Merck colorpHast sticks). The mixture was stirred at ambient temperature for 1 hour, then poured onto a silica gel column (10", 2" id) packed with $CH_2CL_2$ and eluted with 1:1 $Et_2O$:$CH_2Cl_2$. The product fractions were combined and evaporated to dryness in vacuo to provide the title compound as a solid which was recrystallized from petrolium ether and dried 6 hours in vacuo at ambient temperature: (m.p. 146-147°C).

TLC: Rf=0.44 silica gel ($CH_2Cl_2$).
NMR: Consistent with structure.
HPLC: >99.7% pure.
MS: Molecular ion at m/e - 399
Analysis calculated for $C_{23}H_{29}NO_3S$
C, 69.14; H, 7.32; N, 3.51
Found: C, 68.97; H, 7.2; N, 3.38

(1S)-1'-(((7,7-dimethyl-2-oximinobicyclo(2.2.1)hept-1-yl)-methyl)-sulfonyl)spiro(1H-indene-1,4'-piperidine)

(1S)-1'-(((7,7-dimethyl-2-oxobicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)spiro(1H-indene-1,4'piperidine) (30 g, 0.075 mole) in pyridine (500 mL) was heated in an oil bath to 70°C (internal). Hydroxylamine hydrochloride (30 g) was added in three portions over ca. 20 minutes. After 2 hours, an additional 10 g of hydroxylamine hydrochloride was added (over 10 minutes). At 30, 40 and 50 minutes additional elapsed time, further 3 g lots of hydroxylamine hydrochloride were added. After another 30 minutes, the mixture was poured into water (2 L) and extracted 3X with ethyl acetate (300 mL portions). The organic layers were combined, washed with 1N HCl (600 mL total), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. EtOH (abs; ca. 250 mL) was added to the resulting thick syrup and the solution allowed to stand at ambient temperature overnight. The mixture was filtered and the filtrate boiled down to ca. 80 mL. After standing, the mixture was again filtered and boiled down to ca. 20 mL. After a third filtration, the filtered solids were combined to give the title compound (28 g).

Endo-(1S)-1'(((2-amino-7,7-dimethylbicyclo(2.2.1)hept-1-yl)-methyl)sulfonyl)spiro(1H-indane-1,4'-piperidine)

Freshly prepared, activated Raney Nickel catalyst (ca. 30 g) in water was allowed to settle and the water decanted. Abs. ethanol (300 mL) was added, and the mixture swirled and again allowed to settle. The solvent was decanted. Two more wash-decant cycles with 150 mL of ethanol were similarly carried out. (1S)-1'(((7,7-dimethyl-2-oximinobicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine) (30 g) was stirred in a mixture of abs. ethanol (450 mL) and 2-methoxyethanol (900 mL), nitrogen was bubbled through the suspension/solution, and the Raney Nickel catalyst was added. The mixture was hydrogenated under 50 psi overnight. TLC (9:1 $CH_2Cl_2$:-MeOH, silica gel) showed the reaction to be complete. The catalyst was removed by filtration, and the filtrate evaporated to dryness in vacuo.

The crude solid (27 g) was divided into 7 g batches, and each batch was dissolved in methylene chloride (ca. 200 mL) and flash chromatographed on silica (700 g in a 100 mm column, packed and eluted with 8% (v/v) methanol in methylene chloride), taking 200 mL fractions. The exo isomer of the title amine was obtained in fractions ca. 5-7, and the desired endo isomer in fractions ca. 8-16. TLC was on silica, eluted with 8% methanol/methylene chloride, phosphomolybdic acid stain. The combined product fractions were evaporated to dryness to provide the title compound (4.5 g from each 7 g lot, ca 18 g total) as a colorless solid.

Endo-(1S)-1'(((2-(4-imidazoleacetylamino)-7,7-dimethylbicyclo-(2.2.1)-hept-1-yl)methyl)sulfonyl)spiro(1H-indane-1,4'-piperidine hydrochloride

4.56 g (11.3 mmols) of Endo-(1S)-1'(((2-amino-7,7-dimethylbicyclo-(2.2.1)hept-1-yl)methyl)sulfonyl)spiro(1H-indane-1,4'-piperidine) was dissolved in 50 mL DMF and the solution treated with 2.30 g (14.1 mmols) of 4-imidazole acetic acid, 1.9 g (14.1 mmols) of 1-hydroxybenzotriazole hydrate (HBT), and 2.7 g (14.1 mmols) of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl (EDC). The pH of the suspension was adjusted to 9.5 with 4.65 mL (33.4 mmols) of triethylamine and the reaction mixture stirred at 25°C for 18 hours.

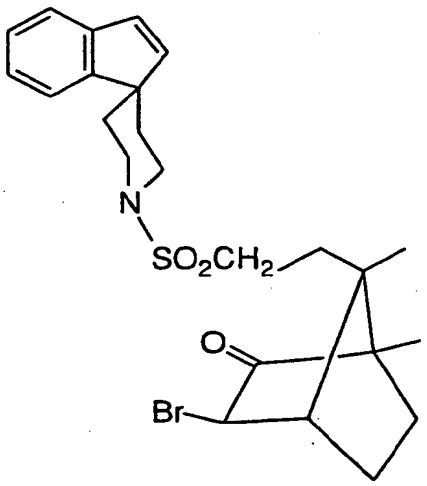
DMF was removed in vacuo and the crude purplish residue treated with water and extracted with EtOAc (3X). The organics were combined, washed with $H_2O$ (1X), brine (1X), dried over $Na_2SO_4$, filtered and stripped to dryness in vacuo. Flash chromatography of the crude product on silica gel (114/10/1 of $CH_2Cl_2$/MeOH/conc. $NH_4OH$) gave 5.29 g (92%) of desired product as a white foam.

5.17 g (10.1 mmols) of this product was dissolved in 100 mL EtOAc. While stirring vigorously, a solution of HCl (g) in EtOAc was added dropwise until precipatation ceased. The slightly gummy mixture was stirred 15 minutes at 25°C, then evaporated to dryness in vacuo. The residue was restripped 3X from EtOAc, then 3X from

$Et_2O$. The white solid was scraped from the walls of the flask, triturated with $Et_2O$ and 5.3 g of hydrochloride salt collected.

M.P.: 93-167°C (slow foam)
HPLC: 99.4%
PMR: Consistent with structure, plus 0.30 ethyl acetate, 0.05 ether and $H_2O$.
M.S.: M+H + 511 (FAB)
Analysis calculated for $C_{28}H_{38}N_4O_3S$ " HCl " 0.30 $C_4H_8O_2$ " 0.05 $C_4H_{10}O$ " 0.4 $H_2O$. (M.W. 584.48)
C, 60.41; H, 7.36; N, 9.59
Found: C, 60.38; H, 7.46; N, 9.33

EXAMPLE 23



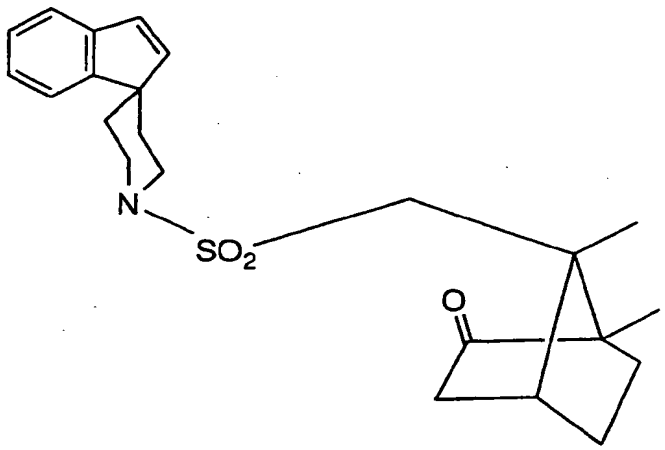

1-[[6-bromo-1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-yl)methyl]-sulfonyl]-spiro[1H-indene-1,4'-piperidine]

Dissolved 100 mg of (+)-3-Bromocamphor-sulfonic acid ammonium salt (.304 mM) in 15 mL of DLM. Added 5 eq of $SOCl_2$ (FW=118.97; d=1.631; 1.52 mM; 120 mL). The mixture was allowed to react overnight, then concentrated to obtain 92.7 mg of the crude sulfonyl chloride. The 92.7 mg of sulfonyl chloride was dissolved in 25 mL of dry THF. To this was added 1.1 eq of indene salt (68.59 mg)

and 2 eq of TFA, which was allowed to react at room temperature for three hours. The product was concentrated and washed with HCl, $H_2O$ and brine. Flask chromatography in 20% EtOAc/petroleum ether.

HPLC 97.7% at 13.52 min.

EXAMPLE 24



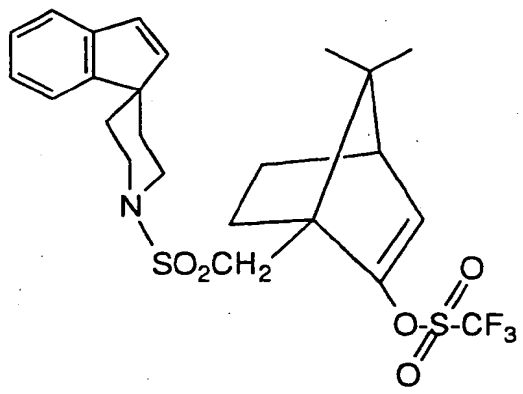

(1R-syn)-1'-[[(1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-yl)methyl)-sulfonyl]-spiro[1H-indene-1,4'-piperidine]

To a solution of the product of Example 23 (107 mg, 0.300 mmol) in glacial acetic acid (10 mL) was added zinc dust (24 mg, 0.367 mmol). The temperature was then increased to reflux. After 30 minutes, the mixture was cooled to room temperature, filtered, then concentrated under reduced pressure. Purification by flash chromatography (35% ethyl acetate in petroleum ether as eluent) afforded 80 mg of the product as a white amorphous foam.

NMR (300 MHz, $CDCl_3$): Consistent with structure.
HPLC (Vydac C18 column, gradient from 95/5 to 0/100 $H_2O/CH_3CN$ with 0.1% TFA, 15 min. gradient, flow rate = 1.5 mL/min): purity = 98%, r.t. = 12.67 min.
FABMS: $[M+1]^+$] at 400.91
Analysis calculated for $C_{23}H_{29}NO_3S$

C, 69.13; H, 7.32; N, 3.51
Found: C, 69.25; H, 7.30; N, 3.48

EXAMPLE 25



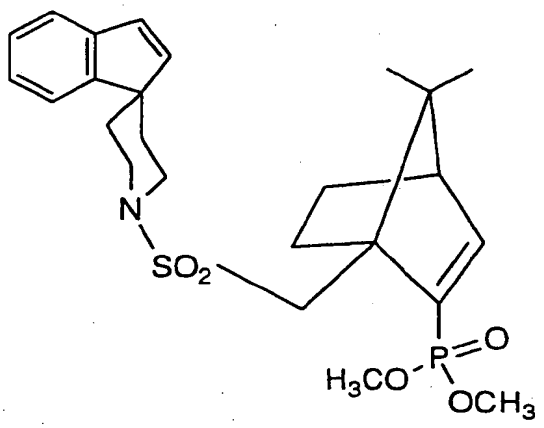

(1S)-1'(((2-(trifluoromethyl)sulfonyl)oxy)2,3-ene-7,7-dimethyl-bicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine)

To a solution of (1S)-1(((7,7-dimethyl-2-bicyclo(2.2.1)-hept-1-yl)methyl)sulfonyl)spiro(1H-indene-1,4'-piperidine) (2g, 5.0 mmol) and 2,6-di-tert-butyl-4-methylpyridine (1.5 g, 7.5 mmol) in $CH_2Cl_2$ (25 ml) was added triflic anhydride (1.3 ml, 7.5 mmol) and the mixture was stirred at room temperature for 30 minutes. The mixture was then diluted with $CH_2Cl_2$ (30 ml) and filtered. The filtrate was then washed with 5% HCl (2x50 ml), saturated $NaHCO_3$ (2x50 ml), and brine, dried over $Na_2SO_4$, and evaporated.

The crude triflate was purified by flash chromatography eluting with 20% ethylacetate in hexanes to yield 1.7 g of the title product as a white foam (64%).

HPLC RT = 12.75 min.
NMR ($CDCl_3$) in agreement with title compound.
FAB MS: 532 (M+1)
Analysis calculated for $C_{42}H_{28}NS_2O_5F_3$
N, 2.63, C, 54.22, H, 2.63
Found: N, 2.37; C, 54.42; H, 5.34

EXAMPLE 26

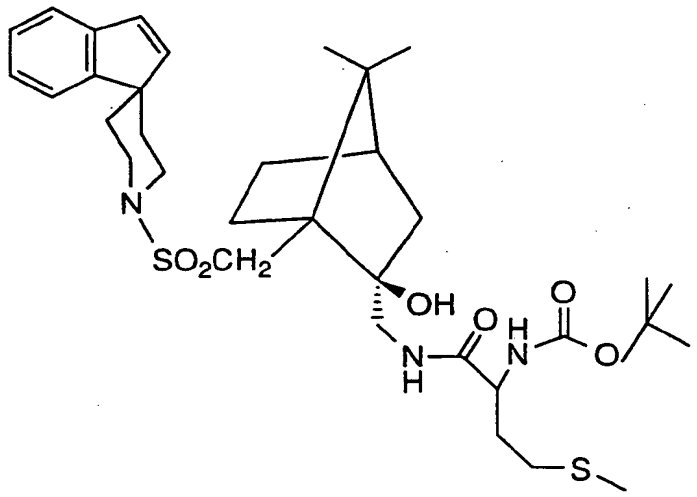



(1S)-1'-(((2-(dimethylphosphonyl)oxy)2,3-ene-7,7-dimethyl-bicyclo(2.2.1)hept-1-yl)sulfonyl)spiro(1H-indene-1,4'-piperidine)

A mixture of the triflate product of Example 25 (50 mg, 0.097 mmol), dimethyl phosphite (13 ml, 0.14 mmol), triethylamine (61 ml, 0.44 mmol), and tetrakis(triphenylphosphine)palladium (5 mg, 0.005 mmol) in DMF (3 ml) was stirred under an atmosphere of argon for 1 hour. The reaction was then diluted with $CHCl_3$ (25 ml). The chloroform was washed with 5% HCl (2x25 ml) and brine, dried over $Na_2SO_4$ and evaporated to dryness. Purification via flash chromatography (25% ethylacetate in hexanes) afforded 40 mg of the title compound as a white solid (86%).

HPLC RT = 10.31 min.
NMR($CDCl_3$) in agreement with title compound
FAB MS: 492 (M+1)
Analysis calculated for $C_{25}H_{34}NSO_5P$ 0.5 $H_2O$
N, 2.80; C, 59.99; H, 7.05
Found: N, 2.71; C, 59.90; H, 7.49

EXAMPLE 27



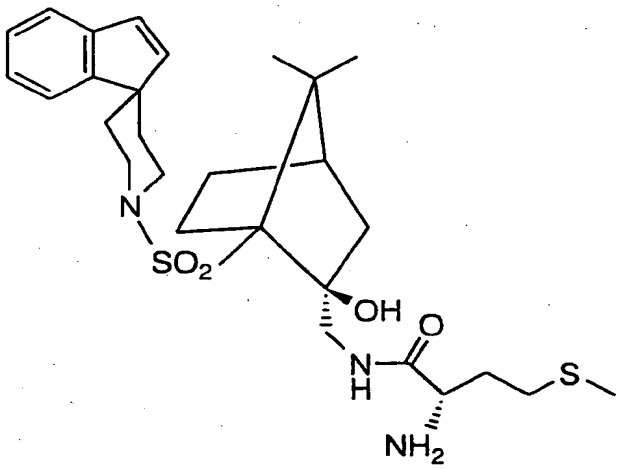
[1-[[[[exo-2-hydroxy-7,7-dimethyl-1-[spiro[1H-indene-1,4-piperidin]-1-yl-sulphonyl)methyl]bicyclo]2.2.1]hept-2-yl]methyl]amino]carbonyl]-3-(methylthio)propyl]-carbamic acid-1,1-dimethylethyl ester

To a stirred solution of (1S)-1'-(((exo-2-hydroxy-endo-2-aminomethyl-7,7-dimethylbicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine) (600 mg, 1.39 mmole) in 5 ml of dry, degassed N,N-dimethylformamide was added Boc-L-methionine (381 mg, 1.53 mmole) and 743 mg (1.68 mmole) of benzotriazol-1-yloxy tris(dimethylamino)phosphonium hexafluorophosphate (BOP) at room temperature. The resulting reaction mixture was protected from moisture and the pH was adjusted to 8-9 with diisopropylethylamine. After one hour, all volatile components were removed under reduced pressure and the residue was dissolved in 250 ml of ethyl acetate. This solution was washed in succession with 10% aqueous citric acid, 50% sodium bicarbonate solution, and brine. The organic phase was dried (sodium sulfate) and concentrated. Chromatography of the crude reaction product on silica gel (1:1 ethyl acetate-hexane elution) afforded the title compound as an amorphous solid: m.p. 82-92°C.

HPLC: >92% pure at 214 nM
NMR: Consistent with structure and verified presence of solvent

FAB MS: 670 ($M^+$ + thioglycerol)
Analysis calculated for $C_{34}H_{51}N_3O_6S_2$ 0.5$CHCl_3$
C, 57.42; H, 7.19; N, 5.82
Found: C, 57.58; H, 7.50; N, 5.83

## EXAMPLE 28

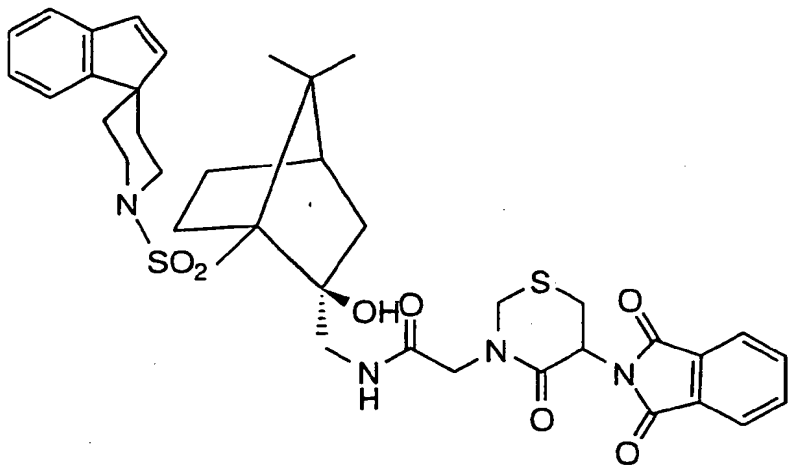



2-amino-N-[[exo-2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]1'ylsulfonyl)methyl]bicyclo]2.2.1]hept-2-yl]methyl]-4-methylthio)-butanamide

A continuous stream of dry HCl gas was passed for 5 minutes into an ice cold solution of ethyl acetate (2 ml) containing 20 mg of the product of Example 27. After 30 minutes at 0°C, the reaction mixture was concentrated and the residue was chromatographed on two 0.25 mm precoated silica gel plates (chloroform-methanol-ammonium hydroxide, 93:7:0.7 v/v elution). The title compound was obtained as a solid (10.7 mg): m.p. 78-80°C.

TLC: Rf=0.28 ($CHCl_3$-$CH_3OH$-$NH_4OH$, 95:5:0.5)
NMR: Consistent with structure and verifies presence of solvent
FAB MS: 562 ($M^+$+H)
Analysis calculated for $C_{29}H_{43}N_3O_4S_2$â0.75$CHCl_3$
C, 54.86; H, 6.77; N, 6.45
Found: C, 54.52; H, 6.90; N, 6.32

EXAMPLE 29



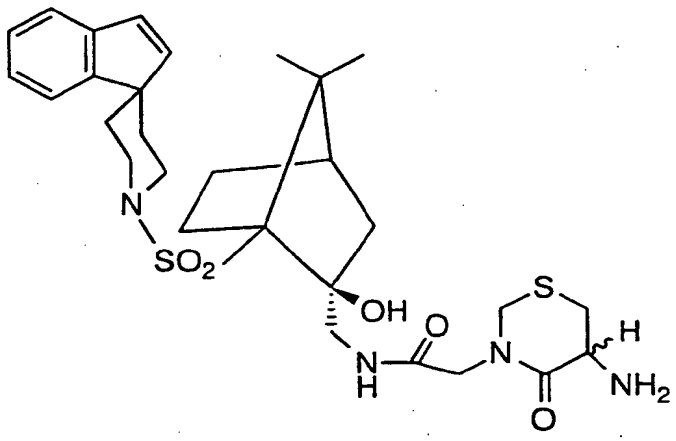
5-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-N-[[2-hydroxy-7,7-dimethy-1-[(spiro[1H-indene-1,4'-piperidin]-1'-ylsulfonyl)methyl]-bicyclo[2.2.1]hept-2-yl]-methyl]dihydro-4-oxo-2H-1,3-Thiazine-3(4H)-acetamide

To a stirred solution of (1S)-1'-(((exo-2-hydroxy-2-aminomethyl-7,7-dimethylbicyclo(2.2.1)hept-1-yl)-sulfonyl)spiro(1H-indene-1,4'-piperidine) (67 mg, 0.16 mmole) in 1.5 ml of dry, degassed N,N-dimethylformamide was added 4-oxo-5-phthalyl-1,3-thiazine-acetic acid (62 mg, 0.192 mmole) and 88 mg (0.20 mmole) of benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) at room temperature. The resulting reaction mixture was protected from moisture and the pH was adjusted to 8-9 with diisopropylethylamine. After 24 hours all volatile components were removed under reduced pressure and the residue was suspended in 5 ml of toluene. Concentration of this suspension afforded the crude product which was chromatographed on silica gel (96:4:0.4 $CHCl_3$-$CH_3OH$-$NH_4OH$) to give the title compound (109 mg): m.p. 134-137° C.

NMR: Consistent with structure and verifies presence of solvent;
HPLC: >94% pure at 214 nM;
FAB MS: 733 ($M^+$+H)

Analysis calculated for $C_{38}H_{44}N_4O_7S_2 1.1CHCl_3$
C, 54.34; H, 5.26; N, 6.48
Found: C, 54.12; H, 5.22; N, 6.42

## EXAMPLE 30

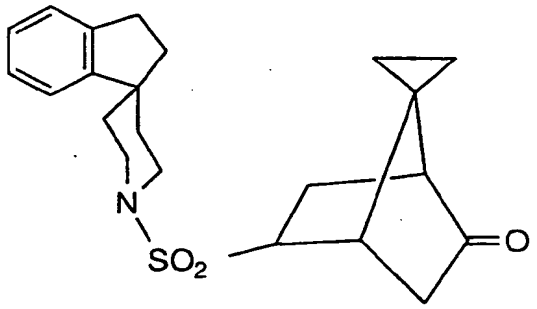


5-amino-N-[[1-[[spiro[1H-indene-1,4'-piperidin]-1-yl)-sulfonyl]-methyl]-exo-2-hydroxy-7,7-dimethylbicyclo-[1.1.1]hept-2-yl]-methyl]dihydro-4-oxo-2H-1,3-Thiazine-3(4H)-acetamide

The product of Example 29 (60 mg) was dissolved in 3 ml of methanol and treated with 50 ml (1.59 mmole) of 95% hydrazine at 23°C. After 24 hours the solvent was removed under vacuum and the residue was suspended in toluene. Rotoevaporation of this suspension gave the crude product, which was chromatographed on four 0.5 mm procoated silica gel plates (chloroform-methanol-ammonium hydroxide, 92:8:0.8 v/v elution). The title compound was obtained as an amorphous solid (27 mg): m.p. 103-106°C.

NMR: Consistent with structure and verifies presence of solvent
HPLC: >97% pure at 214 nM;
FAB MS: 605 ($M^+$+H)
Analysis calculated for $C_{30}H_{44}N_4O_5S_2$ 0.6$CHCl_3$
C, 54.33; H, 6.64; N, 8.28
Found: C, 54.12; H, 6.60; N, 8.20

EXAMPLE 31




1'-[(5-oxospiro[bicyclo[2.2.1]heptane-7,1'-cyclopro-pan]-2-yl)-sulfonyl]-spiro[1H-indane-1,4'-piperidine]

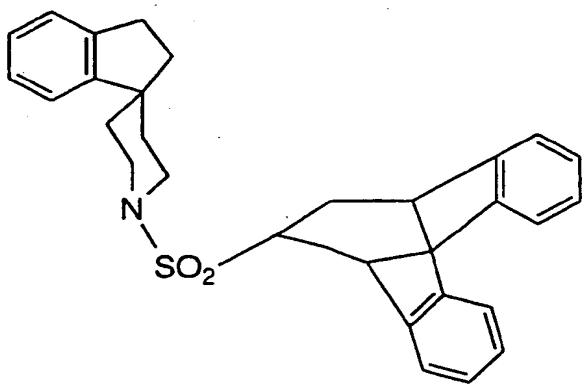
Spiro(1H-indane-1,4'-piperidine)hydrochloride(3 g, 13.5 mmole) was dissolved in 30 ml of methylene chloride. The resulting solution was cooled to 0°C and treated with 3.76 ml of triethylamine. This was followed by the dropwise addition of chloroethyl-sulfonylchloride (1.57 ml, 15 mmole). The reaction mixture was allowed to warm to room temperature over one hour and was filtered. The filtrate was washed with water, sodium bicarbonate solution, and brine. The dried organic washings were concentrated and the residue was column chromatographed on silica gel (98:2 methylene chloride-ether elution) to give 1.88 g of 1'-(vinylsulfonyl)spiro(1H-indane-1,4'piperidine)(m.p. 114-115°C).

1'-(Vinylsulfonyl)spiro(1H-indane-1,4'piperidine) (185 mg, 0.67 mmole) was combined with 5.1 g (55 mmole) of spiroheptadiene in 4 ml of benzene and heated to reflux for 48 hours. The solvent and excess reagent were removed under reduced pressure and the residual oil was chromatographed on silica gel (4:1 hexane-ethyl acetate elution) to give 216 mg of a solid which was recrystallized from methanol to give white needles (m.p. 176-177°C). Of this material, 110.7 mg was dissolved in 5 ml of dry THF under nitrogen. This solution was cooled to 0°C and treated with 0.1 ml of borane-THF complex. After stirring for one hour, an additional 0.1 ml of Borane-THF complex was added to the reaction mixture and stirring was continued at room temperature for 1 hour more. The reaction mixture was recooled to 0°C and

quenched with the dropwise addition of water. After 10 minutes, 0.3 ml of 3N sodium hydroxide solution and 0.3 ml of 30% hydrogen peroxide solution was added. The resulting mixture was heated to 50°C for 1 hour and allowed to stand at 23°C overnight. The reaction mixture was partitioned between ethyl acetate and brine. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the crude reaction product by preparative TLC on silica gel (2:1 hexane-ethyl acetate) afforded two components. The more polar product (m.p. 232-233°C, from methanol) (0.15 mmole) was dissolved in 5 ml of methylene chloride and oxidized with pyridinium chlorochromate (2 mmole) at 23°C. The reaction mixture was filtered through celite and the filtrate was applied to 0.25 mm precoated silica gel plates. Elution with 2:1 hexane-ethyl acetate and recrystallization from methanol afforded the title compound as a white solid: m.p. 210-212°C.

NMR: Consistent with structure and verifies presence of solvent
HPLC: >96% pure at 214 nM;
FAB MS: 386 ($M^+$+H)
Analysis calculated for $C_{22}H_{27}NO_3S0.3CH_20$
C, 67.59; H, 7.12; N, 3.58
Found: C, 67.66; H, 7.22; N, 3.53

EXAMPLE 32

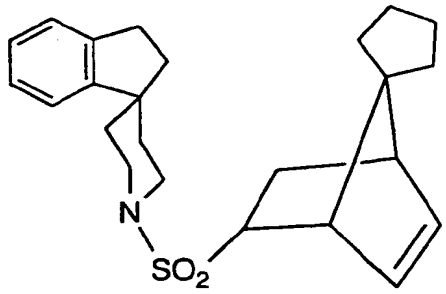


1'-[(9,10-dihydro-9,10-ethanoanthracen-1]-yl)sulfonyl]-spiro[1H-indane-1,4'-piperidine]

1'-(Vinylsulfonyl)spiro(1H-indane-1,4'piperidine) (152 mg) was combined with 350 of anthracene in 15 ml of toluene and heated to reflux for 8 days. The solvent and excess reagent was removed under reduced pressure and the residual oil was chromatographed on silica gel (4:1 hexane-ethyl acetate elution) to give the title compound as an amorphous solid.

NMR: Consistent with structure and verifies presence of solvent
HPLC: >99% pure at 214 nM;
FAB MS: 456 ($M^+$+H)
Analysis calculated for $C_{29}H_{29}NO_2S0.05C\ H_2O\ 0.25\ HCl_3$
C, 72.23; H, 6.08; N, 2.88
Found: C, 72.23; H, 5.92; N, 2.67

EXAMPLE 33



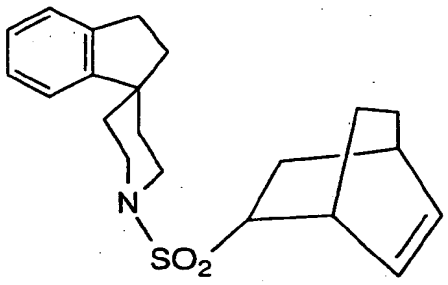

1'-(spiro[bicyclo[2.2.1]hept-5-ene-7,1'-cyclopentan]-2-ylsulfonyl)-spiro[1H-indane-1,4'-piperidine]

1'-(Vinylsulfonyl)spiro(1H-indane-1,4'piperidine) (100 mg) was combined with 500 mg of spirononadiene in 3 ml of toluene and heated to reflux for 17 hours. The solvent and excess reagent were removed under reduced pressure and the residual oil was chromatographed on silica gel (4:1 hexane-ethyl acetate elution) to give the title compound as an amorphous solid: m.p. 115-119°C.

NMR: Consistent with structure and verifies presence of solvent

HPLC: >99% pure at 214 nM;
FAB MS: 398 ($M^+$+H)
Analysis calculated for $C_{24}H_{31}NO_2S0.05CHCl_3$
C, 71.57; H, 7.76; N, 3.47
Found: C, 71.94; H, 7.81; N, 3.42

EXAMPLE 34

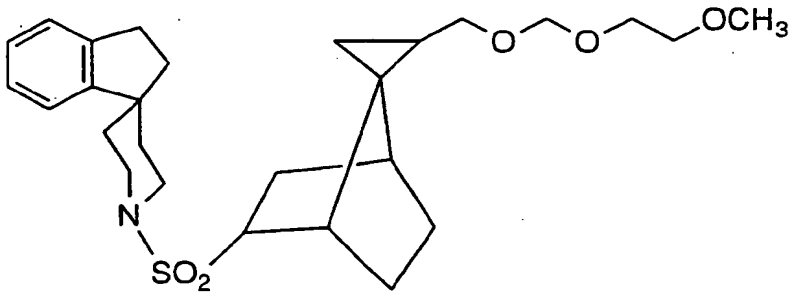



1'-(bicyclo[2.2.1]hept-5-en-2-ylsulfonyl)spiro[1H-indane-1,4'-piperidine]

1'-(Vinylsulfonyl)spiro(1H-indane-1,4'piperidine) (100 mg) was combined with ten equivalents of cyclohexadiene in 10 ml of toluene and heated to reflux for 30 hours. The solvent and excess reagent were removed under reduced pressure and the residual oil was chromagraphed on silica gel (4:1 hexane-ethyl acetate elution) to give the title compound as an amorphous solid: m.p. 162-166°C.

NMR: Consistent with structure and verifies presence of solvent
HPLC: >99% pure at 214 nM;
FAB MS: 358 ($M^+$+H)
Analysis calculated for $C_{21}H_{27}NO_2S0.1H_20$
C, 70.19; H, 7.63; N, 3.90
Found: C, 70.30; H, 8.03; N, 3.61

EXAMPLE 35

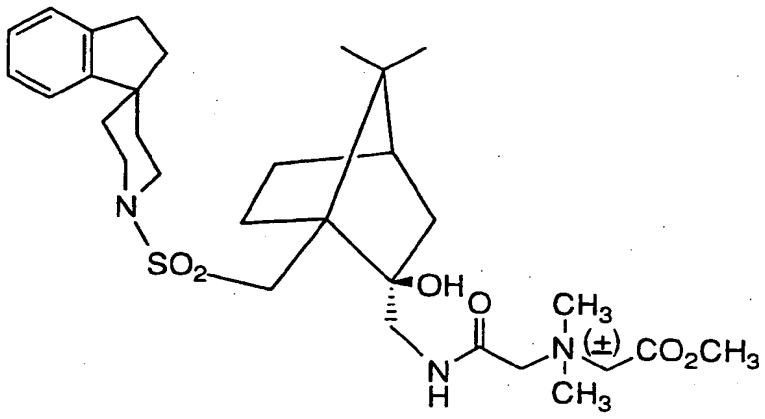



1'-[[2'-[[(2-methoxyethoxy)methoxy]methyl]spiro]bicyclo[2.2.1]hept-5-ene-7,1'-cyclopropan]-2-yl]sulfonyl]-spiro[1H-indane-1,4'-piperidine]

1'-(Vinylsulfonyl)spiro(1H-indane-1,4'piperidine) (2.45 g) was combined with 2.2 g of hydroxymethylspirocycloheptadiene and 3 mg of hydroquinone in 8 ml of toluene and heated to reflux for 17 hours. The solvent and excess reagent were removed under reduced pressure and the residual oil was chromatographed on silica gel (1:2 hexane-ethyl acetate elution) to give three components. The least polar of these products (80 mg) was dissolved in methylene chloride containing 78 mg of diisopropylethylamine and treated with 49 mg of 2-methoxyethoxy-methyl chloride. The reaction mixture was protected from moisture and stirred at 23°C overnight. The reaction mixture was concentrated and the residual material was applied to 0.5 mm precoated silica gel plates. Elution with 1:1 hexane-ethyl acetate afforded the title compound.

NMR: Consistent with structure and verifies presence of solvent;
PLC: >90% pure at 214 nM;
FAB MS: 488 ($M^+$+H)

EXAMPLE 36

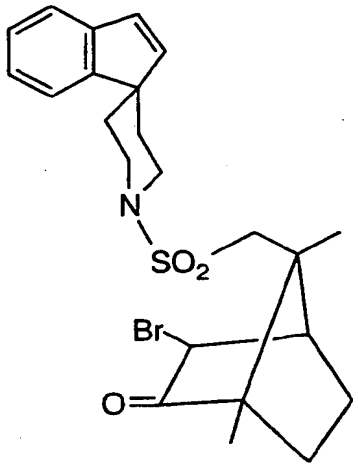


(1S-)-2-[[[exo-2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]-1'-ylsulfonyl)methyl]bicyclo[2.2.1]hept-2-yl]methyl]amino]-N-(2-methoxy-2-oxoethyl)-N,N-dimethyl-2-oxo-ethanaminium salt with trifluoroacetic acid (1:1)

To a stirred solution of (1S)-1'-(((exo-2-hydroxy-endo-2-aminomethyl-7,7-dimethylbicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine) (108 mg, 0.25 mmole) in 5 ml of toluene was added 1 ml of toluene containing 0.5 mmole of methyliminodiacetic acid anhydride. Tetrahydrofuran (2 ml) was added and the white suspension was stirred at 23°C overnight. The reaction mixture was filtered and concentrated. The residue was dissolved in 5 ml of N,N-dimethylformamide and treated in succession with methyl iodide (0.5 ml) and diisopropylethylamine (0.2 ml). The resulting solution was protected from moisture and heated for 5 hours at 50°C. An additional 0.5 ml of methyl iodide was added and heating was continued for 5 hours more. The reaction mixture was concentrated and the residue was purified via reverse phase preparative HPLC (Vydac Protein & Peptide C-18 column, mobile phase = 0.1% trifluoro-acetic acid (TFA) in water-acetonitrile). The fractions containing the title compound were pooled and concentrated. The residue was dissolved in dioxane and this solution was freeze-dried to yield the TFA salt of the title compound as a white powder:

NMR: Consistent with structure and verifies presence of solvent
HPLC: >99% pure at 214 nM;
FAB MS: 588 ($M^+$+H)
Analysis calculated for $C_{31}H_{46}N_3O_6S$ 1.8$CF_3CO_2H$ 1.0 dioxane
C, 52.61; H, 6.27; N, 4.77
Found: C, 52.58; H, 6.40; N, 4.76

EXAMPLE 37

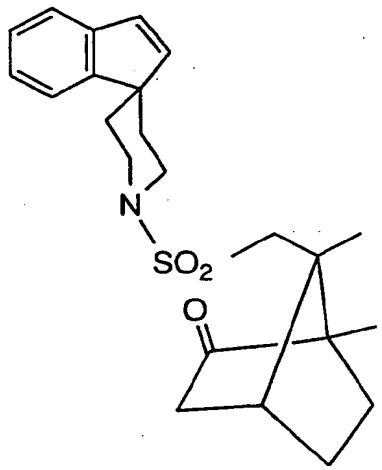



(1R-syn)-1'-[[(1,7-dimethyl-2-oxobicyclo[2.2.1]hept-7-yl)methyl]-sulfonyl]-spiro[1H-indene-1,4'-piperidine]

Dissolved 100 mg (.304 mM; FW=328.23) of (-)-3-bromocamphosulfonic acid ammonium salt in 15 mL of DCM. Added 5 eq of thionylchloride (FW=118.97; d=1.631; 1.52 mM; 120 mL) and allowed mixture to react at 0°C under a $N_2$ balloon for 1 hour. After 1 hour the mixture was concentrated to obtain 63.12 mg of crude acid chloride (.191 mM).

Dissolved 47.13 mg of indene HCl salt in 20 mL of THF. The acid chloride was added along with 2 eq of DIEA, and allowed to react at room temperature for 1 hour, then concentrated and washed with 2 x 200 mL of 1 N NCl, 2 x 200 mL $H_2O$ and 2 x 200 mL brine, then concentrated and dried over sodium sulfate. Flash chromatography in 25% EtOAc/petroleum ether.

EXAMPLE 38

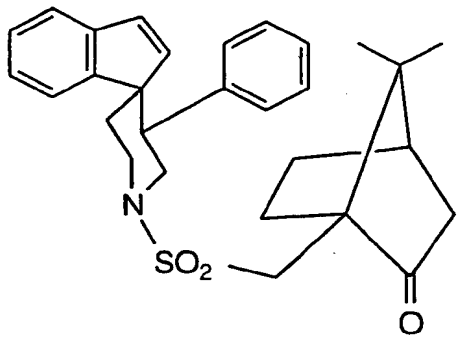



To a solution of the product of Example 37 (107 mg, 0.300 mmol) in glacial acetic acid (10 mL) was added zinc dust (24 mg, 0.367 mmol). The temperature was then increased to reflux. After 30 minutes the mixture was cooled to room temperature, filtered, then concentrated under reduced pressure. Purification by flash chromatography (35% ethyl acetate in petroleum ether as eluent) afforded 80 mg of the product as a white amorphous foam.

NMR (300 MHz, $CDCl_3$): Consistent with structure;
HPLC: (Vydac C18 column, gradient from 95/5 to 0/100 $H_20/CH_3CN$ with 0.1% TFA, 15 min. gradient, flow rate = 1.5 mL/min.):
Purity: 98%, r.t. = 12.67 min.
FAB MS: $[M + 1]^+$ at 400.91

| | |
|---|---|
| Analysis | calculated for $C_{23}H_{29}NO_3S$ |
| | C, 69.13; H, 7.32; N, 3.51 |
| Found: | C, 69.25; H, 7.30; N, 3.48 |

EXAMPLE 39




1'-[[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)-methyl]sulfonyl]-3'-phenyl-spiro[1H-indene-1,4'-piperidine]

Ethanolamine (6.66 mL, 0.1103 mmol) was placed in a 3-neck round bottom flask and heated to reflux. Once at relux, styrene oxide (6.28 mL, 0.0557 mmol) was added dropwise to the reaction mixture over 15 minutes. The reaction mixture was refluxed an additional 2 hours and then allowed to cool. The product, N-(2-hydroxyethyl)-N-(2-hydroxy-2-phenylethyl)amine, was obtained as a clear oil by vacuum distillation.

N-(2-hydroxyethyl)-N-(2-hydroxy-2-phenylethyl)amine (1.30 g, 7.16 mmol) was dissolved in chloroform and then while under a nitrogen blanket, thionyl chloride (1.05 mL, 14.32 mmol) was added dropwise over 10 minutes. The reaction mixture was then refluxed for 1 hour and allowed to cool to room temperature. Water was then added to the mixture and allowed to stir 1 hour. The reaction mixture was separated and the organic layer was washed three times with 3N HCl. The aqueous layers were combined and then basified with 40% sodium hydroxide. The aqueous layer was extracted 3 times with ether, the organics were combined, and dried over sodium sulfate. The organic layer was filtered and the filtrate concentrated to a yellow oil.

The yellow oil was dissolved in ether and then di-t-butyl dicarbonate (1.50 g, 6.87 mmol) was added along with triethylamine (500 ml, 3.59 mmol).The mixture was allowed to stir overnight and then it was washed with $H_2O$ (2x), 0.1N HCl (2x) and sodium bicarbonate (2x). The organic layer was dried over sodium sulfate,

filtered, and the filtrate concentrated to a yellow oil. The yellow oil was dissolved in $CH_2Cl_2$ and poured onto a silica gel column. The column was eluted with 1:1 $CH_2Cl_2$/hexane. The product fractions were combined and concentrated to dryness to yield the product, N-(2-hydroxyethyl)-N-(2-hydroxy-2-phenylethyl)-t-butyl-carbamate.

To a solution of indene (268 ml, 2.30 mmol) in dry THF (2 mL) cooled in an ice bath and maintained under a nitrogen blanket was added lithium bis(trimethylsilyl)amide (1M solution in THF, 4.6 mL, 4.60 mmol) over 10 minutes. The mixture was stirred in the cold bath for 30 minutes, then added over 10 minutes to a solution of N-(2-hydroxyethyl)-N-(2-hydroxy-2-phenylethyl)-t-butylcarbamate (694 mg, 2.30 mmol) stirred in an ice bath. The mixture was stirred for 2 hours in the cold and for 30 minutes at 25°C under nitrogen, then concentrated to an orange oil. 10% ethyl acetate in hexane was added and the resulting mixture poured onto a silica gel column packed with 10% ethyl acetate in hexane. Elution was with the same solvent and the product fraction were concentrated to provide 1'-(t-butyloxycarbonyl)-spiro-(indene-3'-phenyl-1,4'-piperidine.

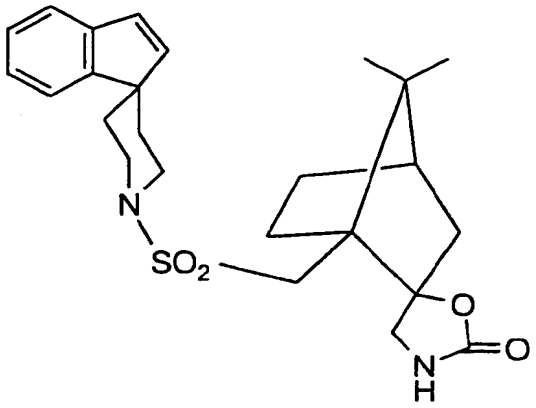
1'-(t-Butyloxycarbonyl)spiro(indene-3-'phenyl-1,4'-piperidine) (290.9 mg, 0.842 mmol) in ethyl acetate was stirred in an ice bath and saturated with HCl (g) for 30 minutes. The mixture was concentrated to dryness and reconcentrated from ether three times to yield spiro (1H-indene-3-phenyl-1,4'-piperidine)-hydrochloride.

Spiro(1H-indene-3'-phenyl-1,4'-piperidine)hydrochloride (205.2 mg, 0.690 mmol) and (+)-10-camphorsulfonyl chloride (196 mg, 0.782 mmol) were combined in THF and the pH was adjusted to 9 with triethylamine (196 mL, 1.41 mmol). The reaction mixture was stirred overnight at 25°C, then concentrated to dryness, and redissolved in $CH_2Cl_2$, then poured onto a silica gel column and eluted with $CH_2Cl_2$. The product fractions were combined and evaporated to dryness to provide the title compound which was crystallized from ether and dried in vacuo overnight.

m.p.: 183° - 215°C

NMR: Consistent with structure
HPLC: >95% pure
MS: M + H 476.3 (FAB)
Analysis calculated for $C_{29}H_{33}NO_3S0.50H_20$
C, 71.86; H, 7.07; N, 2.89
Found: C, 71.88; H, 7.03; N, 2.87

EXAMPLE 40

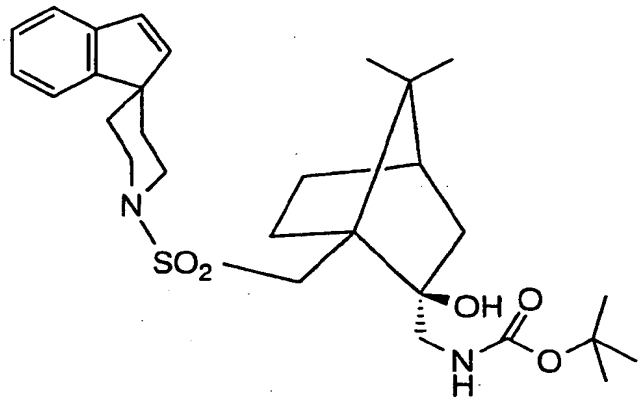



(1S(1a,2a,4a))-2-hydroxy-7,7-dimethyl-1-((spiro-(1H-indene,1,4'-piperidin)-1'-yl-sulfonyl)methyl)-bicyclo-(2.2.1)heptane-2-acetic acid

(100 mg, 0.217 mmol) diphenylphosphoryl azide (51.5 mL, 0.239 mmol), and triethylamine (66.2 mL, 0.471 mmol) were combined in DMF. The mixture was allowed to stir overnight and then it was concentrated to dryness. The resulting residue was dissolved in $CH_2Cl_2$, poured onto a silica gel column, and eluted with 5% methanol in $CH_2Cl_2$. The product fractions were combined and concentrated to dryness. The title compound was obtained as a white solid from ether and dried in vacuo overnight.

NMR: Consistent with structure
HPLC: >93% pure
MS: M + H 457.3 (FAB)
Analysis calculated for $C_{25}H_{32}N_2O_4S$
C, 65.76; H, 7.06; N, 6.14
Found: C, 65.76; H, 7.42; N, 5.80

EXAMPLE 41



(1S-exo)-[[2--hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,2'-piperidin)-1'-ylsulfonyl)methyl]bicyclo2.2.1]hept-2-yl]carbamic acid 1,1-dimethylethyl ester

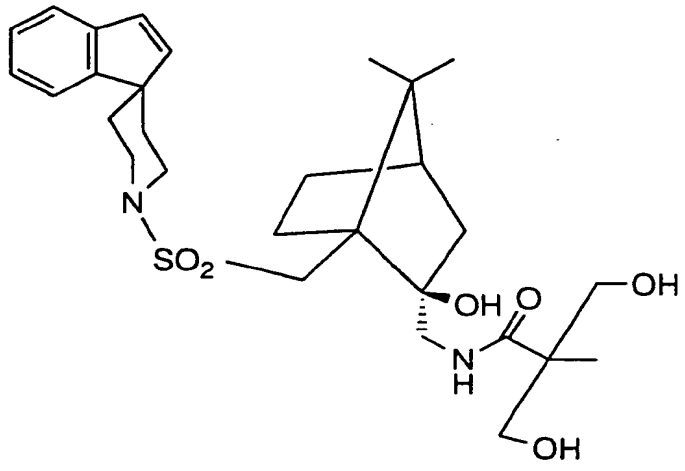
(1S)-1'-(((7,7-dimethyl-2-oxobicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-indene-1,4'-piperidine) (1.92 g, 4.81 mmol) was combined with zinc iodide (47 mg, 0.15 mmol) in 2 mL of toluene. While under a nitrogen atmosphere, the mixture was treated with trimethylsilyl cyanide (960 mL, 7.21 mmol) dropwise. The reaction mixture was then heated to 100°C for 3.5 hours. The mixture was allowed to cool and diluted with 10 mL of dry THF. Then lithium aluminum hydride (1M in THF; 8.6 mL, 8.6 mmol) was added dropwise over 5 minutes and the mixture was allowed to stir at 25°C for 2 hours. The reaction mixture was then diluted with ether (N50 mL) and 10% sodium hydroxide solution was added dropwise until a gray precipitate stopped forming. The mixture was now filtered, the filtrate was washed with sodium bicarbonate and brine, the organic layer was separated and dried over sodium sulfate. The organic layer was filtered, the filtrate concentrated and the residue dissolved in $CH_2Cl_2$. This was poured onto a silica gel column, eluted with 97/3/0.3 of $CH_2Cl_2$/methanol/ ammonium hydroxide and product fractions collected. The product fractions were combined and concentrated to dryness. The desired product, (1S)-1'-(((7,7-dimethyl-(2-endo-aminomethyl-2-exo-hydroxy)-

bicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indene-1,4'-piperidine), was obtained as a white foam from ether.

(1S)-1'-(((7,7-dimethyl-(2-endo-aminomethyl-2-exo-hydroxy)-bicycylo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indene-1,4'-piperidine) (44.9 mg, 0.104 mmol) and di-t-butyl dicarbonate (25 mg, 0.115 mmol) were combined in 5 mL of $CH_2Cl_2$. The reaction mixture was treated with triethylamine (18.1 mL, 0.13 mmol) and then stirred for 30 minutes at 25°C. The reaction mixture was poured onto a silica gel column and eluted with 15% ethyl acetate in hexane. The product fractions were combined and evaporated to dryness. The title compound was obtained as a white solid from $CH_2Cl_2$/hexane and was dried in vacuo overnight.

m.p.: 71°C-115°C
NMR: Consistent with structure
HPLC: >95% pure
Analysis calculated for $C_{29}H_{42}N_2O_5S$ 0.45
C, 66.14; H, 8.73; N, 5.03
Found: C, 66.21; H, 8.52; N, 4.75

## EXAMPLE 42

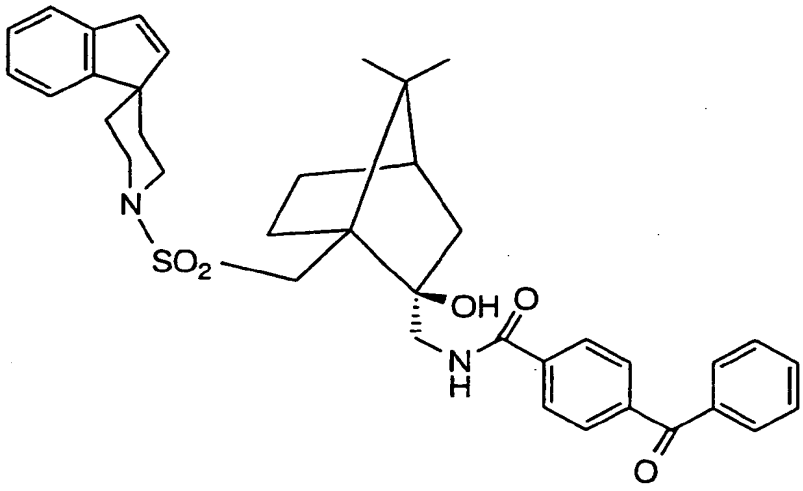


(1S-exo)-3-hydroxy-N-[[2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]-1'-ylsulfonyl)methyl]bicyclo[2.2.1]hept-2-yl]methyl]-2-(hydroxymethyl)-2-methyl-propanamide

(1S)-1'-(((7,7-dimethyl-(2-endo-aminomethyl-2-exo-hydroxy)-bicicylo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indene-1,4'-piperdine) (51 mg, 0.118 mmol), 2,2-bis(hydroxymethyl)-propionic acid (19 mg, 0.142 mmol), 1-hydroxybenzotriazole hydrate (HBT) (19 mg, 0.142 mmol), and 1-ethyl-3-(dimethylaminopropyl) carbodiimideâHCl(EDC) (27 mg, 0.142 mmol) were all combined in 5 mL of DMF. Then, triethylamine (46 mL, 0.33 mmol) was added to adjust the pH to 9, and the mixture was allowed to stir overnight at 25°C. The reaction mixture was concentrated to dryness and treated with 5% citric acid solution. The water layer was then basified with saturated sodium bicarbonate and extracted 3 times with ethyl acetate. The organics were combined and dried over sodium sulfate. The organic layer was filtered, the filtrate concentrated, and the resulting residue dissolved in $CH_2Cl_2$. This was then poured onto a silica gel column and eluted with 3% methanol in $CH_2Cl_2$. The product fractions were combined and evaporated to dryness. The title compound was obtained as a white solid from $CH_2Cl_2$/hexane and was dried in vacuo overnight.

m.p.: 167-170°C
NMR: Consistent with structure
HPLC: >99% pure
MS: M + H 547.3 (FAB)
Analysis calculated for $C_{29}H_{42}N_2O_6S$
C, 63.71; H, 7.74; N, 5.12
Found: C, 63.65; H, 7.59; N, 4.88

EXAMPLE 43



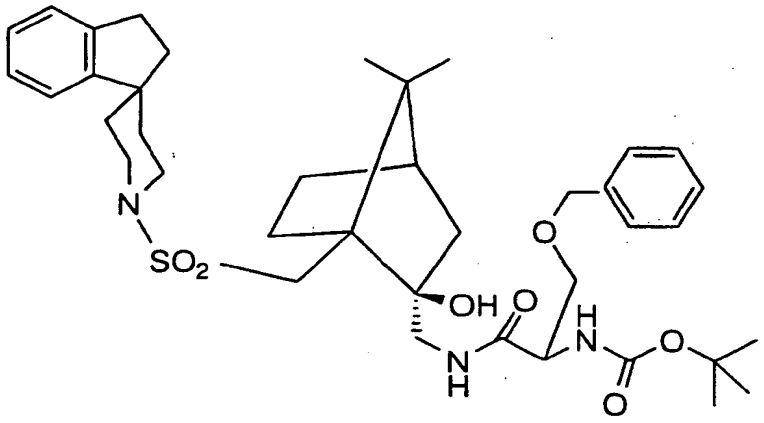
(1S-exo)-4-benzoyl-N-[[2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]-1'-ylsulfonyl)methyl]bicyclo[2.2.1]hept-2-yl]methyl]-benzamide

The procedure of Example 42 was carried out using 49.6 mg, 0.115 mmol of (1S)-(((7,7-dimethyl-(2-endo-aminomethyl-2-exo-hydroxy)-bicicylo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-indene-1,4'-piperidine),26.5 mg, 0.138 mmol of EDC, 18.7 mg, 0.138 mmol of HBT, 48 mL, 0.345 mmol of triethylamine, and substituting 4-benzoylbenzoic acid (31.3 mg, 0.138 mmol) for 2,2-bis-(hydroxy-methyl)-propionic acid. Chromatographic elution was with 2% methanol in $CH_2Cl_2$. The title compound was obtained and dried in vacuo, overnight.

m.p.: 110-135°C
NMR: Consistent with structure
HPLC: >94% pure
MS: M + H 639 (FAB)

| | |
|---|---|
| Analysis | calculated for $C_{38}H_{42}N_2O_5S0.40C_6H_{14}$ |
| | C, 72.06; H, 7.13; N, 4.16 |
| Found: | C, 72.01; H, 7.14; N, 4.18 |

EXAMPLE 44

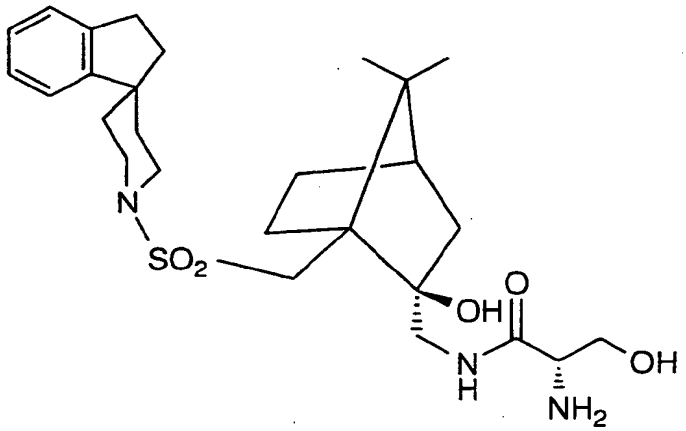


1'-(bicyclo[2.2.1]hept-5-en-2-ylsulfonyl)spiro[1H-indane-1,4'-piperidine]

The procedure of Example 42 was carried out using 94.5 mg, 0.22 mmol of (1S)-(((7,7-dimethyl-(2-endo-amino-methyl-2-exo-hydroxy)-bicicylo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indene-1,4'-piperidine), 49.8 mg, 0.26 mmol of EDC, 35.2 mg, 0.26 mmol of HBT, 90 mL, 0.66 mmol of triethylamine, and substituting t-boc-L-serine(bzl) (76.8 mg, 0.26 mmol) for 2,2-bis-(hydroxymethyl)-propionic acid. Chromatographic elution was with 98/2 of $CH_2Cl_2$/methanol/ammonium hydroxide. The title compound was obtained as a white solid from ether and dried in vacuo overnight.

m.p.: 75-95°C
NMR: Consistent with structure
HPLC: >98% pure
MS: M + H 639 (FAB)
Analysis calculated for $C_{39}H_{53}N_3O_7S$
C, 66.16; H, 7.55; N, 5.94
Found: C, 66.04; H, 7.68; N, 5.84

EXAMPLE 45

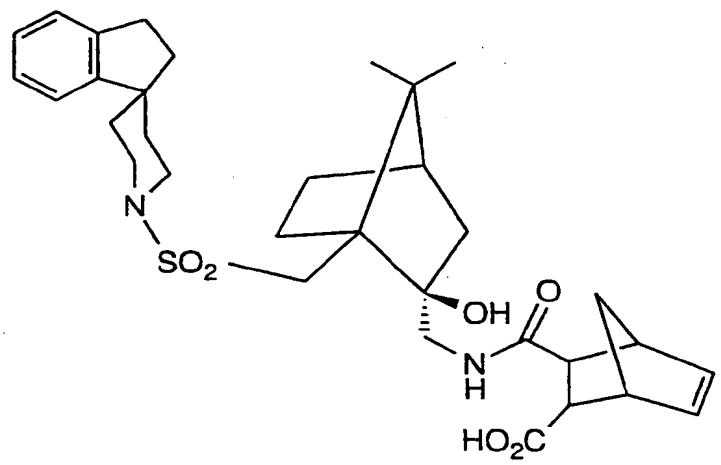


[1S-[1.alpha., 2 Beta., 2(R*), 4. beta.]]-2-amino-N[[1-[[(2,3-dihydro spiro[1H-indene-1,4'-piperidin]-yl)sulfonyl]methyl]-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-2-yl]methyl]-3-hydroxy-propanamide

The product of Example 44 (120 mg, 0.17 mmol) was dissolved in 4% formic acid in methanol. Palladium hydroxide catalyst (25 mg) was added to the solution and it was placed on a PARR apparatus under 50 p.s.i. of hydrogen, overnight. The reaction mixture was filtered over solka floc and the filtrate was concentrated to a clear oil. This clear oil was dissolved in 2 mL of ethyl acetate and chilled to 0°C. At this point, 5 mL of prechilled sat'd HCl/ethyl acetate solution was added dropwise. The reaction mixture was allowed to stir for 1 hour and then concentrated to dryness. The resulting residue was partitioned between ethyl acetate and saturated sodium bicarbonate, and after extracting 3 times with ethyl acetate, the organics were combined and dried over sodium sulfate. The organic layer was filtered, the filtrate was concentrated, and the resulting residue was dissolved in $CH_2Cl_2$. This was then poured onto a silica gel column and eluted with 95/5/0.5 of $CH_2Cl_2$/methanol/ammonium hydroxide. The product fractions were combined and evaporated to dryness. The title compound was obtained as a white solid from ether and dried in vacuo overnight.

m.p.: 70-110°C
NMR: Consistent with structure
HPLC: >93% pure
MS: M + H 520.3 (FAB)
Analysis calculated for $C_{27}H_{41}N_3O_5S0.25\ C_4H_{10}$
C, 61.31; H, 8.20; N, 7.67
Found: C, 61.35; H, 8.11; N, 7.58

EXAMPLE 46



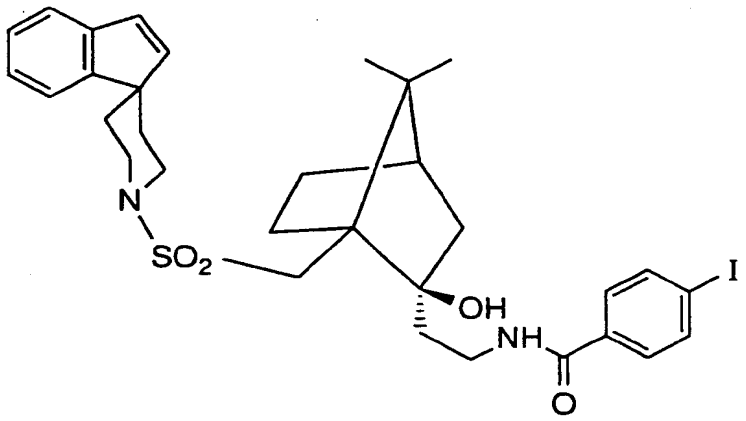

3-[[[[2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]-1'-ylsulfonyl)methyl]bicyclo[2.2.1]-hept-2-yl]methyl]amino]carbonyl]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid

(1S)-(((7,7-dimethyl-(2-endo-aminomethyl-2-exo-hydroxy)-bicicylo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-indene-1,4'-piperidine) (98.5 mg, 0.23 mmol) was combined with bicyclo (2.2.1)-5-heptene-2,3-dicarboxylic anhydride (43 mg, 0.26 mmol) in 5 mL of THF. Triethylamine (50 mL, 0.36 mmol) was added to the reaction dropwise to adjust the pH to 9. The reaction mixture was stirred overnight and then concentrated to dryness. The resulting residue was dissolved in $CH_2Cl_2$, poured onto a silica gel column, and eluted with 97/3/0.3 of chloroform/methanol/acetic acid. The product fractions were combined and concentrated to dryness. The title

compound was obtained as a white solid from ether and dried in vacuo overnight.

m.p.: 128-165°C
NMR: Consistent with structure
HPLC: >95% pure
MS: M + H 595 (FAB)
Analysis calculated for $C_{33}H_{42}N_2O_6S0.10\ CH_2Cl_2$
C, 64.74; H, 7.12; N, 4.56
Found: C, 64.76; H, 7.07; N, 4.66

EXAMPLE 47




(1S)-1'-(((2-endo-cyanomethyl-7,7-dimethyl-exo-2-hydroxybicyclo-(2.2.1)-hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine)

Lithium bis(trimethylsilyl)amide (21.3 ml of a 1.0M THF solution, 21.3 mmol) was cooled to -78°C under $N_2$, treated with acetonitrile (1.07 ml, 20.4 mmol) and stirred 15 minutes. A THF solution (30 mL) of (1S)-1'-(((7,7-dimethyl-2-oxobicyclo(2.2.1)-hept-1-yl)methyl)sulfonyl)spiro(1H-indene-1,4'-piperidine) (40 gm, 10 mmol) was added dropwise and stirred 10 minutes after addition was complete. 6N HCl (2.8 ml) was added to the cold reaction all at once and the mixture was allowed to warm to 25°C.

The mixture was diluted with $H_2O$ (25 ml) and extracted with EtOAc (3 x 100 ml). The organic layers were combined, washed

with $H_2O$ (25 ml) and brine (25 ml), dried over $Na_2SO_4$, filtered and concentrated to dryness in vacuo. Trituration with ether gave the title compound (4.17 gm, 93% yield) as a crystalline solid (m.p. 199-202°C).

TLC: $R_f$ = 0.69, Silica GF (7% $Et_2O$ in $CH_2Cl_2$)
PMR : Consistent with structure

(1S)-1'-(((2-endo-aminoethyl-7,7-dimethyl-2-exo-hydroxybicyclo-(2.2.1)-hept-1-yl)methyl)sulfonyl)spiro(1H-indene-1,4'-piperidine)

Under a blanket of nitrogen, Lithium Aluminum Hydride (8.0 ml, 8.0 mmol, of a 1.0 M THF solution) was cooled to 0°C, treated dropwise with a THF solution (37 ml) of (1S)-1'-(((2-endo-cyano-methyl-7,7-dimethyl-2-hydroxybicyclo-(2.2.1)-hept-1-yl)methyl)-sulfonyl)spiro(1H-indene-1,4'-piperidine) (4.4 gm, 10.0 mmol) and the reaction stirred 10 minutes. With rapid stirring, the reaction was treated with $H_2O$ (0.37 ml), 20% NaOH (aq) (0.40 ml) and $H_2O$ (1.46 ml) followed by extraction with EtOAc (3 x 150 ml). The organic layers were combined, washed with $H_2O$ (25 ml) and brine (25 ml), dried over $Na_2SO_4$, filtered and concentrated to dryness in vacuo.

Flash chromatography on silica gel (90/10/1/1 of $CH_2Cl_2$/MeOH/$H_2O$/HOAc) provided product fractions which were pooled and concentrated to dryness. The residue was treated with sat'd $Na_2CO_3$ (aq) and extracted with EtOAc (3 x 100 ml). The organic layers were combined, washed with $H_2O$ (25 ml) and brine (25 ml), dried over $Na_2SO_4$, filtered and concentrated to dryness to give the title compound (2.55 gm, 57% yield) as a white foam/solid.

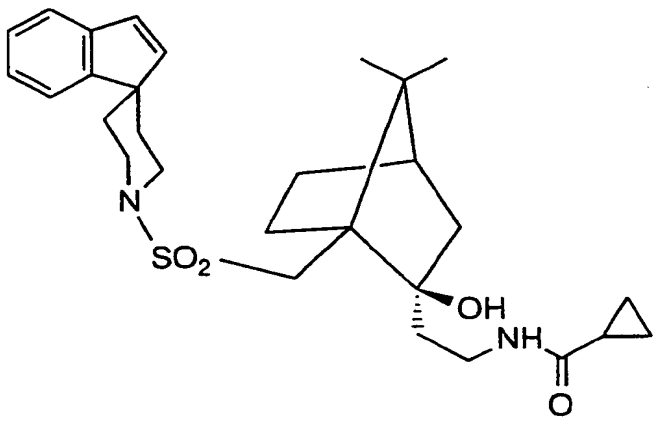
TLC: $R_f$ = 0.27 Silica GF (90/10/1/1 of $CH_2Cl_2$/MeOH/$H_2O$/HOAc)
PMR: Consistent with structure

(1S)-1'-(((2-endo-aminoethyl-7,7-dimethyl-2-exo-hydroxybicyclo-(2.2.1)-hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine) (60 mg, 0.135 mmol) was dissolved in $CH_2Cl_2$ (1 ml), treated with 4-iodobenzoyl chloride (36.0 mg, 0.135 mmol) and $Et_3N$

to adjust the pH to 9.5. The reaction was stirred 30 minutes at 25°C and flash chromatographed on silica gel (8% $Et_2O$ in $CH_2Cl_2$) to give the title compound (45 mg, 50% yield) as a white foam from $Et_2O$ (m.p. 98-138°C, shrinks).

TLC: $R_f$ = 0.35 Silica GF (10% $Et_2O$ in $CH_2Cl_2$)
PMR: Consistent with structure
HPLC: 95.8% pure
M.S.: (FAB) M + H + Thioglycerol = 783
Analysis calculated for $C_{32}H_{39}IN_2O_4S0.30C_4H_{10}O;0.35\ H_2O$
C, 56.70; H, 6.12; N, 3.98
Found: C, 56.73; H, 6.11; N, 4.01

## EXAMPLE 48



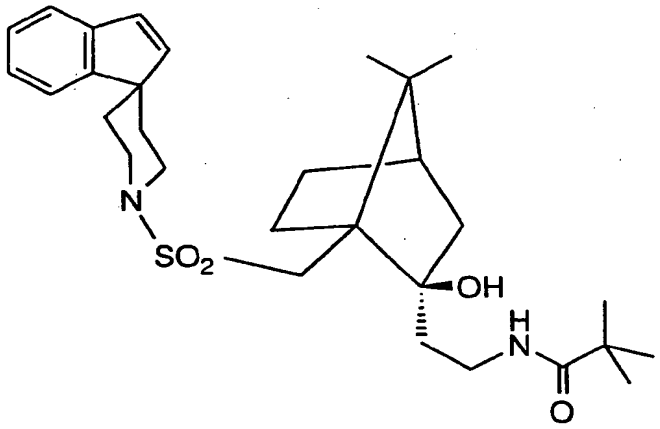

(1S-exo-N-[2-[2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]1'-ylsulfonyl)methyl]bicyclo[2.2.1]hept-2-yl]ethyl]-cyclopropanecarboxamide

The title compound was prepared according to the procedure of Example 47 except that cyclopropylcarbonyl chloride (12.4 ml, 0.135 mmol) was substituted for 4-iodobenzoyl chloride.

Flash chromatography of the reaction mixture on silica gel (15% $Et_2O$ in $CH_2Cl_2$) gave the title compound (36.6 mg, 53% yield) as a white foam from Ether (m.p. 93-105°C shrink + foam).

TLC: $R_f$= 0.22 Silica GF (15% $Et_2O$ in $CH_2Cl_2$)
PMR: Consistent with Structure
HPLC: 96.8%
M.S.: (FAB) M + H + Thioglycerol = 621
Analysis calculated for Calc'd for $C_{29}H_{40}N_2O_4S0.20C_7H_{10}O$
C, 67.84; H, 8.03; N, 5.31
Found: C, 67.69; H, 8.06; N, 5.06

EXAMPLE 49




(1S-exo)-N-[2-[2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin[-1'-ylsulfonyl)Methyl]bicyclo[2.2.1]hept-2-yl]ethyl]-2,2-dimethyl-propanamide

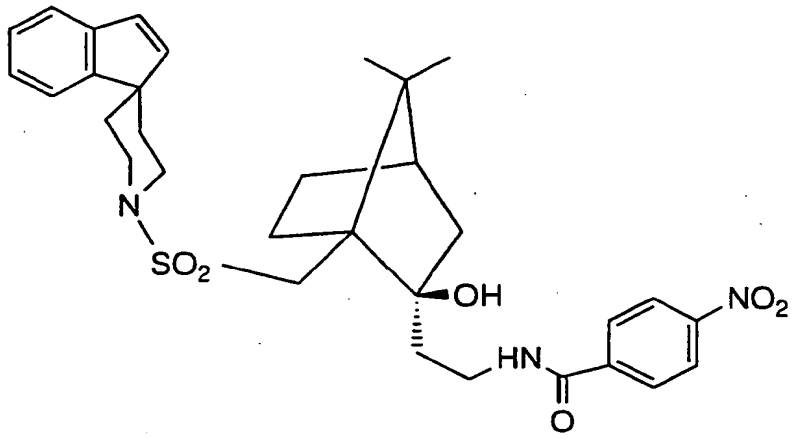
The title compound was prepared according to the procedure of Example 47 except that trimethyl acetyl chloride (16.6 ml, 0.135 mmol) was substituted for 4-iodobenzoyl chloride.

Flash chromatography of the reaction on silica gel (13% $Et_2O$ in $CH_2Cl_2$) gave the title compound (32.8 mg, 46% yield) as a white foam from $Et_2O$ (m.p. 78-104°C, shrink + foam).

TLC: $R_f$ = 0.29 Silica GF (15% $Et_2O$ in $CH_2Cl_2$)
PMR: Consistent with structure
HPLC: 97.6%
M.S.: (FAB) M + H + Thioglycerol = 637
Analysis calculated for $C_{30}H_{44}N_2O_4S0.20C_4H_{10}O0.30\ H_2O$ =

C, 67.38; H, 8.56; N, 5.10
Found: C, 67.37; H, 8.52; N, 5.02

EXAMPLE 50



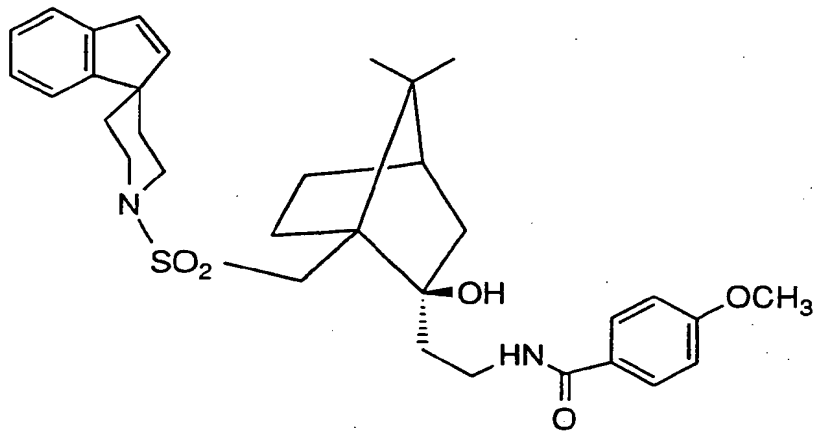

(1S-exo)-N-[2-[2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]-1'-ylsulfonyl)methyl]bicyclo[2.2.1]hept-2-yl]ethyl]-4-methoxy-benzamide

The title compound was prepared according to the procedure of Example 47 except that 4-nitrobenzoyl chloride (25.1 mg, 0.135 mmol) was substituted for 4-iodobenzoyl chloride.

Flash chromatography of the reaction on silica gel (10% $Et_2O$ in $CH_2Cl_2$) gave the title compound (41.6 mg, 52% yield) as a white foam from Ether (m.p. 118-33°C, shrink + foam).

TLC: $R_f$= 0.26 Silica GF (10% $Et_2O$ in $CH_2Cl_2$).
PMR: Consistent with structure
HPLC: 97.1%
M.S.: (FAB) M + H + Thioglycerol = 702.
Analysis calculated for $C_{32}H_{39}N_3O_6S0.30C_4H_{10}O0.20\ H_2O$
C, 64.35; H, 6.90; N, 6.78
Found: C, 64.32; H, 6.98; N, 6.63

EXAMPLE 51



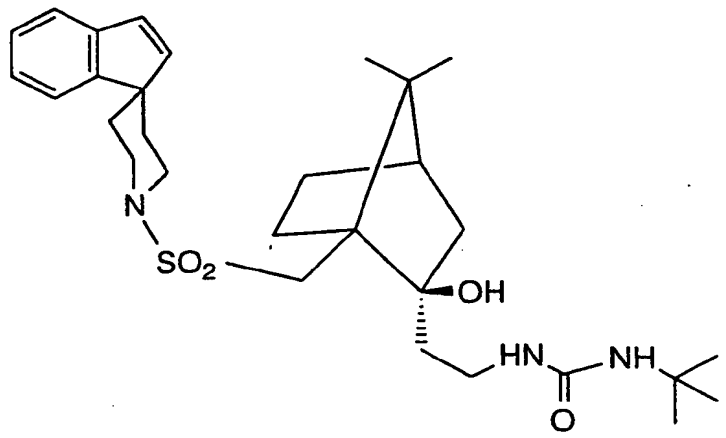

(1S-exo)-N-[2-[2-hydroxy-7,7-dimethyl-1-[(spiro[1H-indene-1,4'-piperidin]-1'-ylsulfonyl)methyl]ethyl]bicyclo[2.2.1]hept-2-yl]ethyl[-4-methoxy-benzamide

The title compound was prepared according to the procedure of Example 47 except that p-anisoyl chloride (18.3 ml, 0.135 mmol) was substituted for 4-iodobenzoyl chloride.

Flash chromatography of the reaction on silica gel (15 % $Et_2O$ in $CH_2Cl_2$) gave the title compound (36 mg, 46% yield) as a white solid from $Et_2O$ (m.p. 98-121°C, shrink).

TLC: $R_f$= 0.26 Silica GF (15% $Et_2O$ in $CH_2Cl_2$).
PMR: Consistent with structure
HPLC: 95.5%
M.S.: M + H + Thioglycerol = 687
Analysis calculated for $C_{33}H_{42}N_2O_5S0.25\ C_4H_{10}O$
C, 68.36; H, 7.51; N, 4.69
Found: C, 68.14; H, 7.67; N, 4.55

EXAMPLE 52



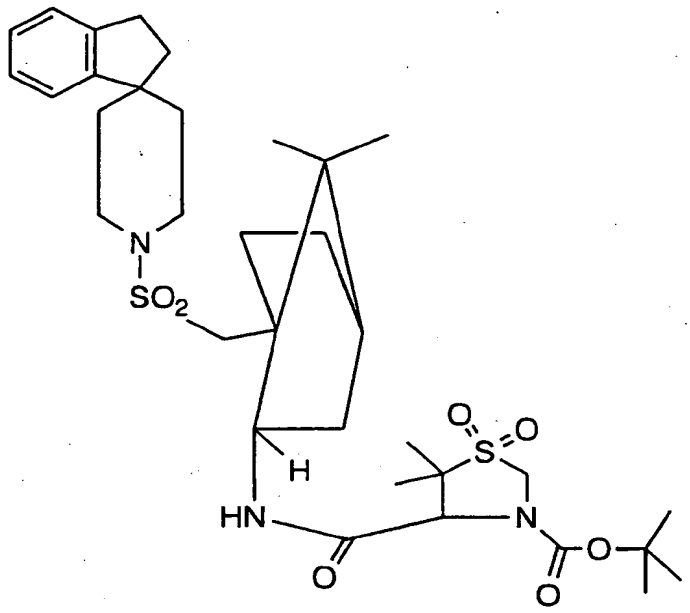

(1S-exo)-1'-[[[2-[2-[[[(1,1-dimethylethyl)amino]-carbonyl]amino]-ethyl]-2-hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-yl]methyl]-sulfonyl]-spiro[1H-indene-1,4'-piperidine]

(1S)-1'-[[[endo-aminoethyl-7,7-dimethyl-exo-hydroxy-bicyclo(2.2.1)-hept-1-yl]methyl]sulfonyl]spiro(1H-indene-1,4'-piperidine) (60 mg, 0.135 mmol) was dissolved in THF (2 ml), treated with t-butyl isocyanate (15.4 ml, 0.135 mmol) and stirred 30 minutes at 25°C.

After removal of the solvent in vacuo, the residue was flash chromatographed on silica gel (25% $Et_2O$ in $CH_2Cl_2$ to give the title compound (27.9 mg, 38% yield) as a white solid from $Et_2O$ (m.p. 97-119°C, shrink and foam).

TLC: $R_f$= 0.21 Silica GF (20% $Et_2O$ in $CH_2Cl_2$)
PMR: Consistent with structure
HPLC: 95.1%
M.S.: (FAB) M + H + Thioglycerol = 652
Analysis calculated for $C_{30}H_{45}N_3O_4S0.25C_4H_{10}O0.30\,H_2O$
C, 65.58; H, 8.54; N, 7.40
Found: C, 65.70; H, 8.74; N, 7.05

EXAMPLE 53



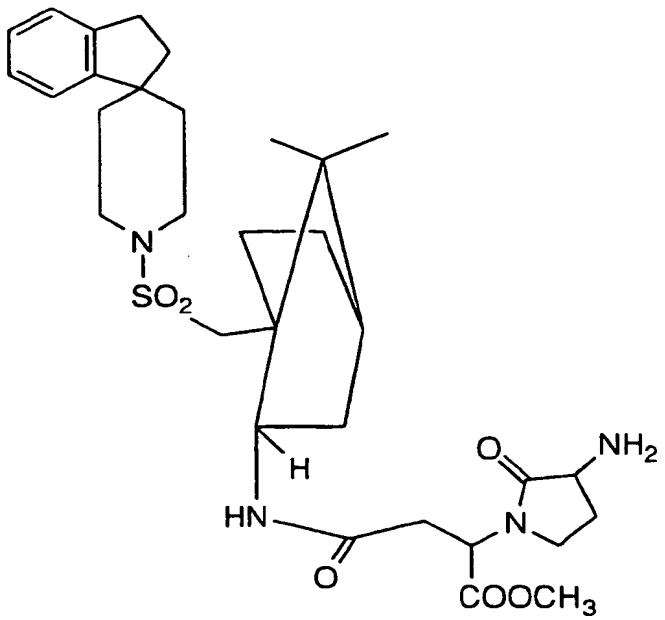

To a stirred solution of 10 ml of dry N,N-dimethyl-formamide containing endo(1S)-1'-(((2-amino-7,7-dimethyl-bicyclo(2.2.1) hept-1-yl)methyl)sulfonyl)-spiro(1H-indane-1,4'-piperidine) (670 mg, 1.66 mmole) and $N^a$-tert-butyloxycarbonyl-5,5-dimethyl-L-thiazolidine-4-carboxylic acid (500 mg, 1.91 mmole) was added 932 mg (2.11 mmole) of benzotriazol-1-yloxytris (dimethyl-amino)phosphonium hexafluorophosphate. The pH of the reaction mixture was adjusted to 8.5 with diisopropylethylamine and the reaction mixture was stirred at 23°C overnight. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and this solution was washed in succession with saturated sodium bicarbonate solution (3 X 25 ml) and brine. The organic phase was dried (sodium sulfate) and concentrated to yield a brown solid which was purified by chromatography on silica gel (chloroform-methanol-concentrated ammonium hydroxide elution, 98:2:0.2 v/v) to yield a white solid. This material was dissolved in 10 ml of chloroform. The solution was cooled in an icebath and treated dropwise with a solution of 5 ml of chloroform containing 2.2

equivalents of m-chloroperoxy-benzoic acid. After addition was complete the ice bath was removed and stirring was continued for 24 hours. The reaction mixture was diluted to 100 ml with choroform and was washed with 1M sodium hydroxide solution (2 X 30 ml) and brine. The organic phase was dried (sodium sulfate) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (chloroform-methanol-concentrated ammonium hydroxide elution, 98:2:0.2 v/v) to yield the title compound:

NMR: Consistent with structure and verifies presence of solvent;
HPLC: >94% pure at 214 nM;
FAB MS: 678 ($M^+ + H$);

| | |
|---|---|
| Elem Analysis | calculated for $C_{34}H_{51}N_3O_7S_2 \cdot 0.8CHCl_3$ |
| | C, 54.04; H, 6.75; N, 5.43 |
| Found: | C, 54.11; H, 6.64; N, 5.48 |

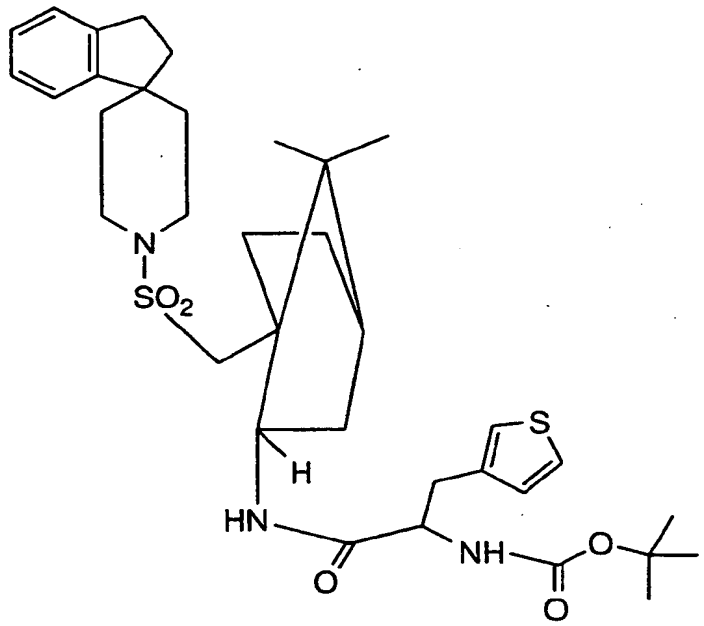
EXAMPLE 54



Endo(1S)-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)spiro(1H-indane-1,4'-piperidine)(660 mg, 2.05 mmole) and (S)-3-[(tert-butyloxycarbonyl)amino]-2-oxo-1-pyrrolidine-(R)-2-methylcarboxysuccinic acid (826.5 mg, 2.05 mmole) were combined with 392 mg (2.05 mmole) of 1-ethyl-3-(3-dimethylamino-propyl) carbodiimide hydrochloride and 275 mg (2.05 mmole) of 1-hydroxybenzotriazole hydrate in 20 ml of dry methylene chloride at room temperature under nitrogen. The pH of the reaction mixture was adjusted to 8.5 with triethylamine and the resulting solution was stirred for 12 hours. The reaction mixture was diluted with methylene chloride (150 ml) and the resulting solution was washed with saturated sodium bicarbonate solution (2 X 40 ml), 10% citric acid solution (2 X 40 ml), and brine, then dried (magnesium sulfate) and concentrated to give the crude product. The analytically pure material was obtained via preparative HPLC chromatography employing a Vydac C-18 column (4.5 X 150 mm, water-acetonitrile-1% trifluoroacetic acid 45 minute gradient). The homogeneous fractions containing product were pooled and concentrated. The residue was dissolved in methylene chloride containing trifluoroacetic acid (50%)at room temperature. After 2 hours, the volatiles were removed under reduced pressure to yield the title compound as a trifluoroacetate salt:

NMR: Consistent with structure and confirms presence of solvent;
HPLC: > 97% pure at 214 nm;
FAB MS: 615 ($M^+ + H$);
Elem Analysis calculated for $C_{34}H_{47}F_3N_4O_8S \cdot 0.3\ H_2O \cdot 0.8TFA$:
C, 51.59; H, 5.88; N, 6.74.
Found: C, 51.59; H, 5.89; N, 6.81.

EXAMPLE 55

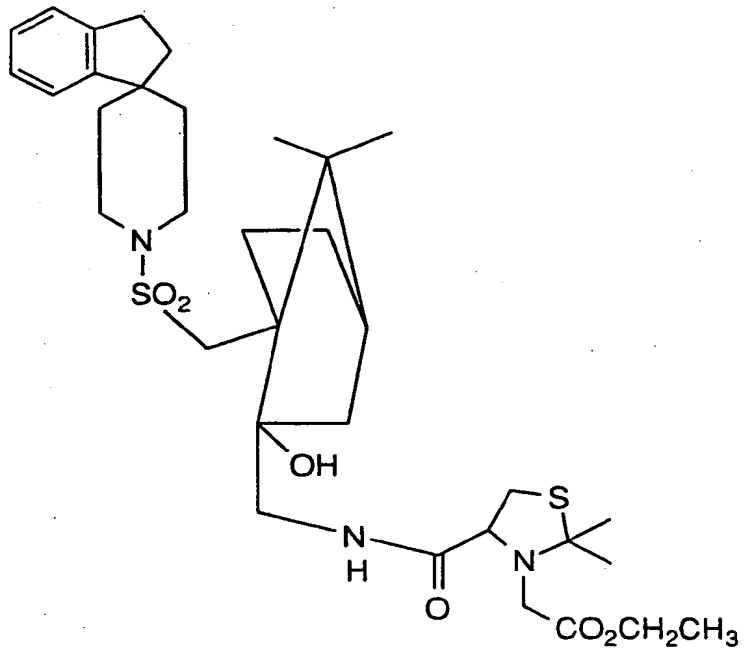



Endo-(1S)-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1) hept-1-yl)methyl)sulfonyl)spiro(1H-indane-1,4'-piperidine)(216 mg, 0.53 mmole) and $N^a$-tert-butyloxycarbonyl-D,L-(3-thienyl)alanine (160 mg, 0.59 mmole) were combined with 113 mg (0.59 mmole) of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and 79 mg (0.59 mmole) of 1-hydroxybenzotriazole in 6 ml of dry methylene chloride at room temperature under nitrogen. The pH of the reaction mixture was adjusted to 9 with triethylamine and the resulting solution was stirred for 12 hours. An additional 20 mg of tert-butyloxycarbonyl-D,L-(3-thienyl)alanine, 11 mg of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride were added and stirring was continued for 6 hours more keeping the pH of the medium between 8 and 9. The reaction mixture was diluted with methylene chloride (150 ml) and the resulting solution was washed with saturated sodium bicarbonate solution (2 X 40 ml), 10% citric acid solution (2 X 40 ml), and brine, then dried (magnesium sulfate) and concentrated to give the crude product. The analytically pure material was obtained via flash column

chromatography on silica gel (chloroform-methanol-concentrated ammonium hydroxide elution, 95:5:0.5 v/v) :

NMR: Consistent with structure and confirms presence of solvent;
HPLC: > 99% pure at 214 nm;
FAB MS: 656 ($M^+ + H$);
Elem Analysis calc'd for $C_{35}H_{49}N_3O_5S_2 \cdot 0.5\ H_2O$:
C, 63.22; H, 7.58; N, 6.32.
Found: C, 63.26; H, 7.54; N, 6.10.

EXAMPLE 56

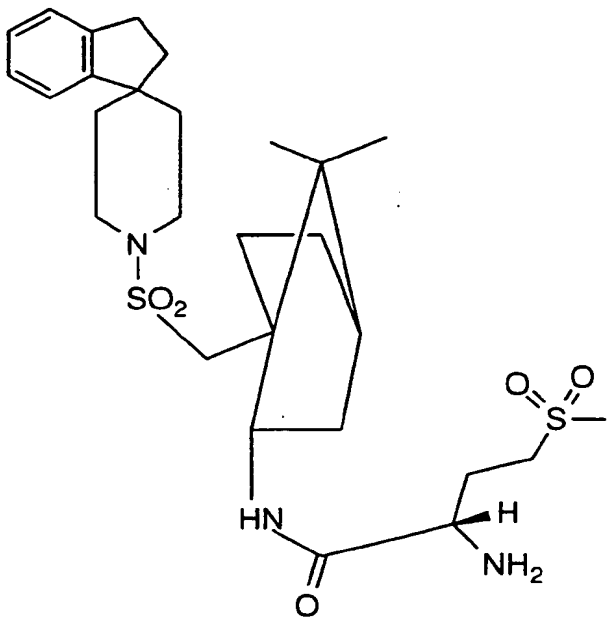



Endo(1S)-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1) hept-1-yl)methyl)sulfonyl)spiro(1H-indane-1,4'-piperidine)(67 mg, 0.156 mmole) and N-ethyl-carboxymethyl-5,5-dimethyl-L-thiazolidine-4-carboxylic acid (57 mg, 0.23 mmole) were combined with 44 mg (0.23 mmole) of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and 31 mg (0.23 mmole) of 1-hydroxybenzotriazole

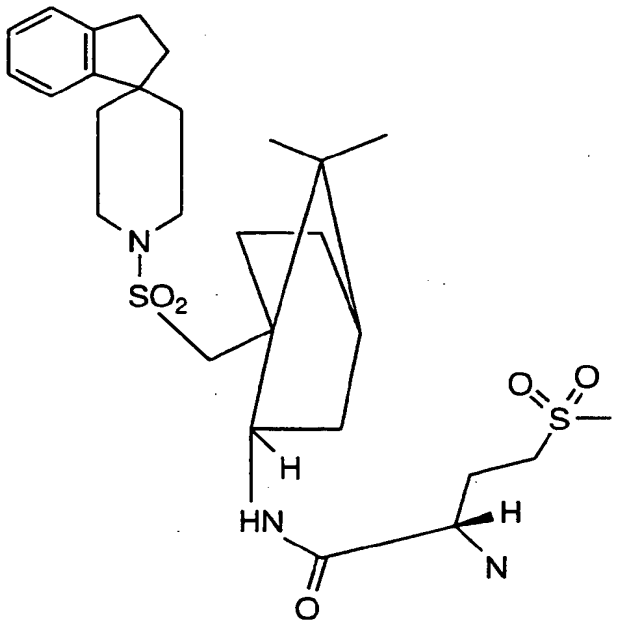
hydrate in 5 ml of dry methylene chloride at room temperature under nitrogen. The pH of the reaction mixture was adjusted to 8.5 with triethylamine and the resulting solution was stirred for 3 hours. The reaction mixture was diluted with methylene chloride (50 ml) and the resulting solution was washed with saturated sodium bicarbonate solution (2 X 40 ml), 10% citric acid solution (2 X 40 ml), and brine, then dried (magnesium sulfate) and concentrated to give the crude product. The analytically pure material was obtained via preparative thick layer chromatography (2 X 20 X 20 mm, pre-coated $SiO_2$ plates, hexane-ethyl acetate elution, 2:1 v/v). The analytical product was isolated in homogeneous form as a solid:

NMR: Consistent with structure and confirms presence of solvent;
FAB MS: 660 ($M^+ + H$);
Elem. Analysis calc'd for $C_{34}H_{47}N_3O_6S_2 \cdot 0.85\ H_2O \cdot 0.1EtOAc$:
C, 60.40; H, 7.59; N, 6.14.
Found: C, 60.37; H, 7.36; N, 6.13.

EXAMPLE 57



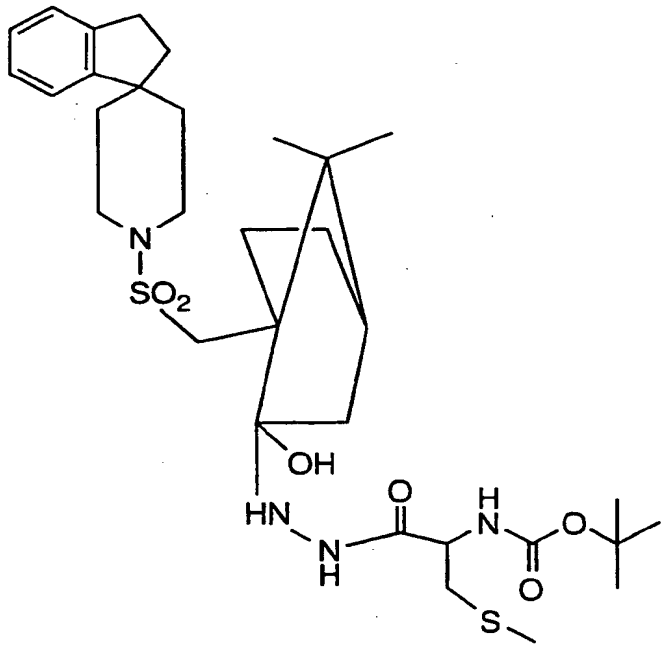
To a stirred solution of 50 ml of dry N,N-dimethylformamide containing endo(1S)-1'-(((2-amino-7,7-dimethylbicyclo(2.2.1) hept-1-yl)methyl) sulfonyl)spiro(1H-indane-1,4'-piperidine) (4.0g, 9.9 mmole) and Na-tert-butyloxycarbonyl-L-methioninesulfone (2.84 g, 11.9 mmole) was added 5.65 g (12.87 mmole) of benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate. The pH of the reaction mixture was adjusted to 8.5 with diisopropylethylamine and the reaction mixture was stirred at 23°C for two hours. The reaction mixture was filtered and concentrated under reduced pressure to give a solid. This material was dissolved in ethyl acetate and this solution was washed in succession with saturated sodium bicarbonate solution (3 X 25 ml), 10% citric acid solution (3 X 25 ml) and brine. The organic phase was dried (sodium sulfate) and concentrated to yield 2-tert-butyloxycarbonylamino-N-[1-[[(2,3-dihydrospiro[1H-indene-1,4'-piperidin]-1'-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-4-(methylsulfonyl)-butanamide which was purified by chromatography on silica gel (chloroform-methanol-concentrated ammonium hydroxide elution, 95:5:0.5 v/v) to yield a solid. This material was dissolved in 50 ml of ethyl acetate and the resulting solution was cooled to 0°C and treated with a continuous stream of hydrogen chloride gas for 15 minutes. The ice bath was removed, the reaction vessel was capped, and stirring was continued for 45 minutes more at room temperature. The solvent and excess hydrogen chloride were removed under reduced pressure to give 2-amino-N-[1-[[(2,3-dihydrospiro[1H-indene-1,4'-piperidin]-1'-yl)-sulfonyl]methyl]-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl]-4-(methyl-sulfonyl)butanamide hydrochloride as an off-white solid (6.5 g).



2-amino-N-[1-[[(2,3-dihydrospiro[1H-indene-1,4'-piperidin]-1'-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-4-(methylsulfonyl)-butanamide hydrochloride was chromatographed on silica gel (chloroform-methanol-concentrated ammonium hydroxide elution, 90:10:1 v/v) to afford a white solid which was dissolved in 15 ml of methanol containing 1% acetic acid. To this reaction mixture was added 3 ml of aqueous formaldehyde solution and 1.56 g (24.8 mmole) of sodium cyanoborohydride. The resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The phases were separated and the organic phase was washed with brine, dried (sodium sulfate), and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (chloroform-methanol-concentrated ammonium hydroxide elution, 95:5:0.5 v/v) to yield 2-dimethylamino-N-[1-[[(2,3-dihydrospiro[1H-indene-1,4'-piperidin]-1'-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-4-(methylsulfonyl)butanamide:

NMR: Consistent with structure and verifies presence of solvent;
HPLC: >98% pure at 214 nM;
FAB MS: 594($M^+$ + H);
Elem. Analysis calc'd for $C_{30}H_{47}N_3O_5S_2 \cdot 0.1CHCl_3$:
C, 59.67; H, 7.84; N, 6.94.
Found: C, 59.90; H, 7.24; N, 6.93.

EXAMPLE 58

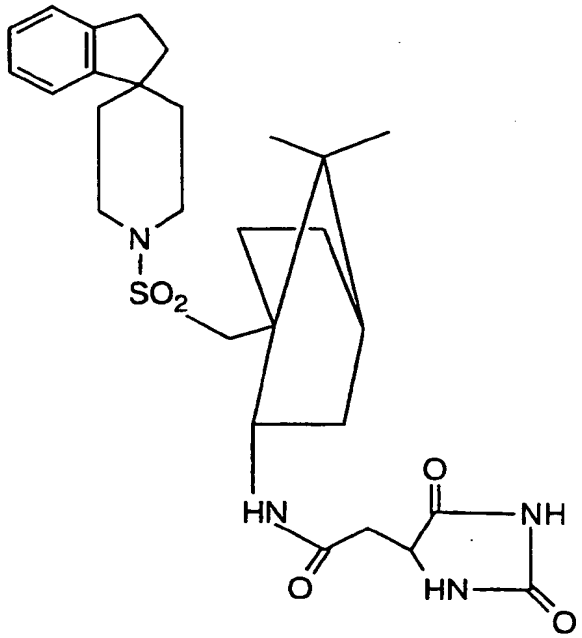



To a stirred solution of (1S)-1'-(((2-exo-hydroxy-2-endo-aminomethyl-7,7-dimethylbicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine) (300 mg, 0.694 mmole) in 10 ml of dry, degassed N,N-dimethylformamide was added $N^a$-tert-butyloxy-carbonyl-S-methyl-L-cysteine (212 mg, 0.832 mmole) and 398 mg (0.902 mmole) of benzotriazol-1-yloxy tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) at room temperature. The resulting reaction mixture was protected from moisture and the pH was adjusted to 8-9 with diisopropylethylamine. After 24 hours all volatile

components were removed under reduced pressure and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The phases were separated and the organic phase was washed with saturated sodium bicarbonate solution (3 X 40 ml) and brine, then dried (magnesium sulfate) and concentrated. The crude product was chromatographed on silica gel (hexane-ethyl acetate elution, 3:1 v/v) to give the title compound:

NMR: Consistent with structure and verifies presence of solvent;
HPLC: >98% pure at 214 nM;
FAB MS: 650 ($M^+$ + H);
Elem. Analysis calc'd for $C_{33}H_{50}N_3O_6S_2$:
C, 61.07; H, 7.71; N, 6.47.
Found: C, 61.24; H, 7.98; N, 6.13.

EXAMPLE 59



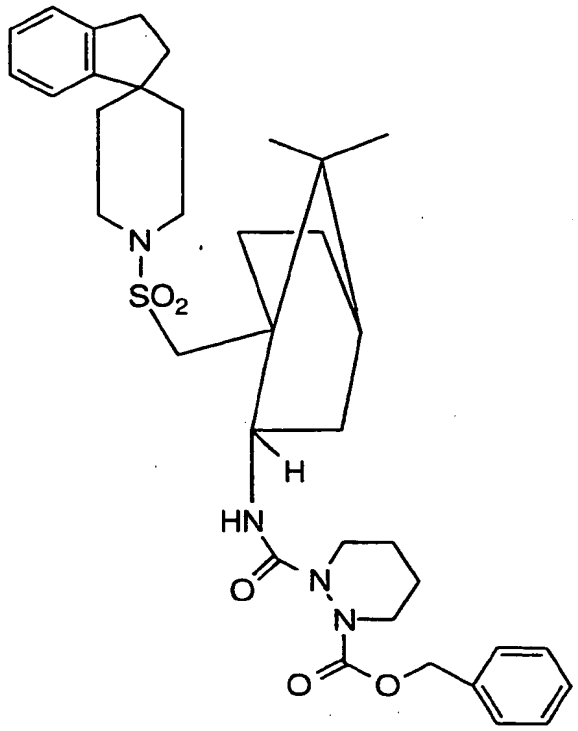

To a stirred solution of (1S)-1'-(((2-exo-hydroxy-2-endo-aminomethyl-7,7-dimethylbicyclo(2.2.1)hept-1-yl)methyl)sulfonyl)-spiro(1H-indene-1,4'-piperidine) (125 mg, 0.311 mmole) in 7 ml of

dry, degassed N,N-dimethylformamide was added S-hydantoinacetic acid (59 mg, 0.372 mmole) and 178 mg (0.404 mmole) of benzotriazol-1-yloxy tris(dimethylamino)phosphonium hexafluorophosphate (BOP) at room temperature. The resulting reaction mixture was protected from moisture and the pH was adjusted to 8-9 with diisopropyl-ethylamine. After 24 hours all volatile components were removed under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and sodium bicarbonate solution. The phases were separated and the organic phase was washed with saturated sodium bicarbonate solution (3 X 40 ml) and brine, then dried (magnesium sulfate) and concentrated. The crude product was initially flash chromatographed on silica gel (chloroform-methanol elution, 96:4, v/v) to give semi-pure material from which the title compound was obtained as a white solid after preparative thick layer chromatography on silica gel (chloroform-methanol-concentrated ammonium hydroxide elution, 96:4:0.4, v/v) and trituration with ether-petroleum ether:

NMR: Consistent with structure and verifies presence of solvent;
FAB MS: 543 ($M^+ + H$);

| | |
|---|---|
| Elem. Analysis | calculated for $C_{28}H_{48}N_4O_5S$ |
| | C, 61.96; H, 7.00; N, 10.32 |
| Found: | C, 61.70; H, 7.36; N, 10.09 |

EXAMPLE 60



(1S)-1'-(((7,7-dimethyl-2-endo-(4-nitrophenyloxycarbonylamino)-bicyclo-(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine

(1S)-1'-(((7,7-dimethyl-(2-endoamino)-bicyclo(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-indene-1,4-piperdine)[3.47mmol] and 4-Nitrophenyl chloroformate [3.64mmol] were combined in THF. The reaction mixture was treated with triethylamine [4.54 mmol] and allowed to stir for 3 hours. The reaction mixture was concentrated to dryness and the resulting residue was purified by a silica gel column, while eluting with 1% ethylacetate in methylene chloride. The product fractions were combined and concentrated to dryness in vacuo. (1S)-1'-(((7,7-dimethyl-(4-nitrophenyloxycarbonyl-2-endoamino)-bicyclo-(2.21)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indene-1,4'-piperidine was obtained as a white solid from ether.

(1S)-1'-(((7,7-dimethyl-2-endo-(4-nitro-phenyloxy-carbonylamino)-bicicylo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-

indene-1,4'-piperdine)-[0.278mmol] and (benzyloxycarbonyl) piperazic acid [0.334mmol] were combined in DMF. The reaction mixture was treated with triethylamine [0.401mmol] and allowed to stir for 2 hours. The reaction mixture was concentrated to dryness and the resulting residue was dissolved in $CH_2Cl_2$. This solution was placed on a silica gel column and eluted with 5% methanol in $CH_2Cl_2$ and then with 96/4/0.4 of $CH_2Cl_2$/methanol/acetic acid. The product fractions were combined and evaporated to dryness. The title compound was obtained as a white solid from ether and was dried in vacuo overnight.

m.p.: 90-120°C

NMR: Consistent with structure

HPLC: >98% Pure

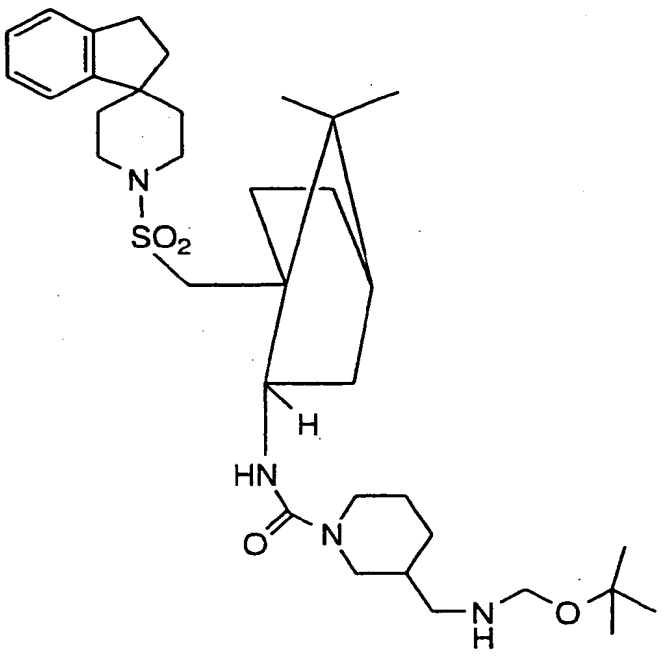
MS: M-->$H^+$=693.6

Analysis calculated for $C_{37}H_{48}N_4O_7S \cdot 0.20mol$ $C_4H_{10}O \cdot 0.25mol\ H_2O$

C, 63.74; H, 7.15; N, 7.87

Found: C, 63.78; H, 7.08; N, 7.81

EXAMPLE 61



The procedure of Example 60, second paragraph was carried out using (1S)-1'-(((7,7-dimethyl-2-endo-(4-nitrophenyloxy-carbonylamino)-bicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)spiro(1H-indan-1,4'-piperidine)[0.193mmol], triethylamine [0.29mmol], and substituting 3-(t-butoxycarbonylamino-methyl)piperidine [0.212mmol] for (benzyloxycarbonyl) piperazic acid. Chromatographic elution was with 5% ether in $CH_2Cl_2$, 10% ether in $CH_2Cl_2$, and then 1% methanol in $CH_2Cl_2$. The title compound was obtained from ether and dried in vacuo, overnight.

m.p.: 95-105°C

NMR: Consistent with structure

HPLC: >97% Pure

MS: $M+H^+=643.4$

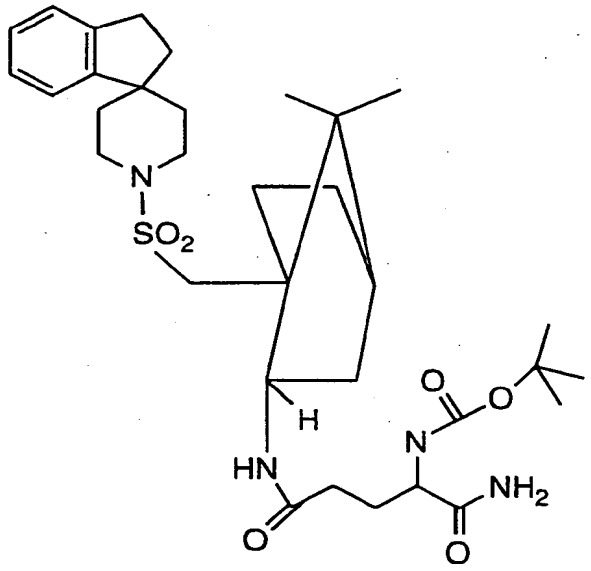
Analysis calculated for $C_{35}H_{54}N_4O_5S \cdot 0.20\ H_2O$

C, 65.02; H, 8.48; N, 8.67

Found: C, 64.98; H, 8.43; N, 8.86

EXAMPLE 62

Endo-(1S)-1'-(((2-(L-4(tert,butoxycarbonylamino)glutaramyl)amino-7,7-dimethylbicyclo(2.2.1)hept-1-yl)-methyl)-sulfonyl)spiro-(1H)-indan-1,4',piperidine



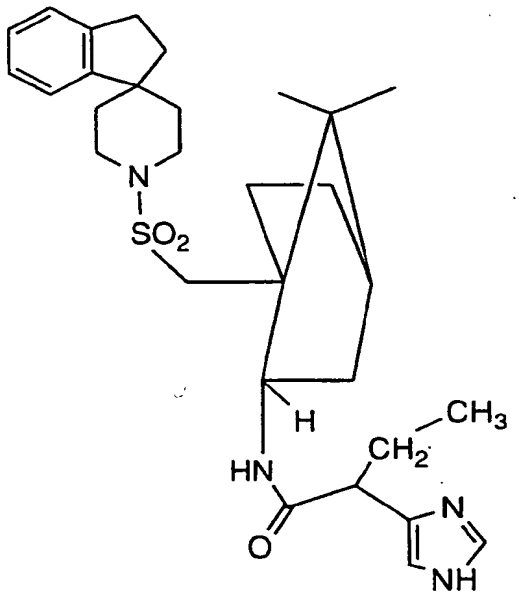

In an oven dried flask (50ml) under nitrogen was dissolved endo-(1S)-1'-(((2-amino-7,7-dimethyl-bicyclo(2.2.1)hept-1-yl)-methyl)-sulfonyl)spiro-(1H)-indan-1,4'-piperidine (50mg, 0.125mmol), L-4(tert-butoxycarbonyl)glutaramic acid (34mg, 0.14mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (30mg, 0.15mmol), and 1-hydroxybenz-triazole hydrate (20mg 0.15mmol) in dimethyl formamide (1ml). Triethylamine (50ml) was added and a white solid separated. After stirring for 1 hour, the solvent was removed under reduced pressure. The residue was dissolved in ether:methylene chloride (3:1). The cloudy solution was washed with sodium bicarbonate (sat., aqueous), water, potassium hydrogen sulfate (10%, aqueous) and brine. After drying over sodium sulfate, the organic material was filtered and concentrated. Silica "flash" chromatography using methylene chloride methanol (9:1) gave the product which was isolated as an oil upon evaporation of the solvents. Hexane:ether

addition and removal under reduced pressure produced the title compound as a white foam.

HPLC: >99%
MS: $M+H^+$=631.3
NMR consistent with structure
Analysis calculated for $C_{33}H_{50}N_4O_6S \cdot 0.5$ DMF$\cdot 0.5$ $H_20$
C, 61.26; H, 8.12; N, 9.32
Found: C, 61.27; H, 8.05; N, 9.31

## EXAMPLE 63

Endo-(1S)-1'-(((2-(4(imidazole-2-ethylacetyl)amino-7,7-dimethyl-bicyclo(2.2.1)hept-1-yl)-methyl)spiro-(1H)-indan-(1,4'),piperdine hydrochloride




Step 1: Endo-(1S)-1'-(((2-4(3-methylbenzyloxy)imidazole)-2-[ethyl acetyl)amino-7,7-dimethylbicyclo- (2.2.1)hept-1-yl)-methyl)-sulfonyl)spiro(1H)-indan-(1,4')-piperidine

Into an over dried flask (50ml) under nitrogen was placed dimethylformamide (4ml). Endo(1S)-1'-((2-amino-7,7-dimethyl-

bicyclo(2.2.1)hept-1-yl)-methyl)sulfonyl)spiro(1H)-indan-(1,4')-piperidine (300mg,0.74mmol), 4(3-methylbenzyloxy)imidazole-2-ethylacetic acid (219mg, 0.8mmol), 1-ethyl-3-methyl-(3-dimethyl-aminopropyl)carbodiimidehydrochloride-(153mg, 0.8mmol) and 1-hydroxybenztriazolehydrate-(108mg, 0.83mmol) were added and the mixture was stirred until solution was achieved. Triethylamine (400ml) was added to make the solution basic (pH 9) and a solid separated. After stirring overnight room temperature, the solvent was removed under reduced pressure. The resulting gum was dissolved in methyenechloride:ether (1:3) and the cloudy solution was extracted with sodium bicarboante (sat., aqueous) and brine. After drying the organic layers over sodium sulfate, the solution was filtered and was concentrated. The product was purified by silica gel "flash" chromatography using methylene chloride, methanol, ammonium hydroxide (9:1:1) as solvents. The product fractions were concentrated to give the title compound as white foam.

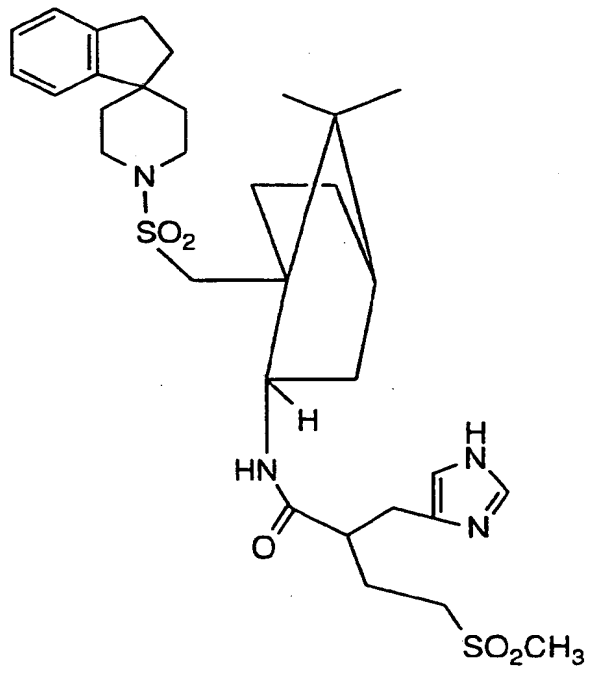
HPLC: >95% (42% + 53%)
MS: $M+H^+$=659.3
NMR ($CDCl_3$) consistent with structure
Analysis calculated for $C_{38}H_{50}N_4O_4S \cdot 0.65H_2O$
C,68.05; H,7.71; N,8.36
Found: C,68.03; H,7.87; N,8.60

Nitrogen was bubbled into a solution of Endo(1S)-1'-(((2-4-(3-methylbenzyloxyimidazole)-2-ethylacetylamino-7,7-dimethyl-bicyclo(2.2.1)hept-1-yl)-methyl)-sulfonyl)spiro-(1H)-indan-(1m4')piperidine (50mg, 0.076mmol) in absolute ethanol (20ml)-acetic acid (5ml). After 5 minutes, 10%Pd/C(50mg) was added and the mixture was hydrogentated at 55psi overnight. The catalyst was removed by filtration and the solvents were concentrated to dryness under reduced pressure. The residue was purified by silica gel "flash" chromatography using methylenechloride, methanol,ammonium hydroxide (9:1:1) as solvent. The product fractions were collected and concentrated. The gum was redissolved in methylene chloride and was

filtered through a sintered glass funnel. After the solution was concentrated, the residue was dissolved in ethyl acetate (5ml). The solution was cooled to 0° and it was saturated with hydrogen chloride gas (bubbling 5 minutes). The solvent was removed under reduced pressure and ether was added and was removed to give the title compound as a white solid.

HPLC: >90% (42% + 45%)
MS: $M+H^+$=539.2 (freebase)
NMR ($CDCl_3$) consistent with structure
Analysis calculated for $C_{30}H_{42}N_4O_3S \cdot HCl \cdot 0.25$ ether$\cdot 130H_2O$
C, 60.33; H, 7.86; N-9.08
Found: C, 60.33; H, 7.48; N-9.04

EXAMPLE 64




To a stirred solution of the product of Example A (500 mg, 1.24 mmol) in DMF (10 mL) was added the HCl salt of 2-(1-benzyloxy-methylimidazoly-5-yl)-4-methylsulfonylbutanoic acid (506 mg; 1.30

mmol), DIEA (0.70 mL; 4.0 mmol), and BOP (600 mg; 1.35 mmol). After being stirred at ambient temperature for 14 h, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (75 mL) and washed with aqueous $NaHCO_3$ (3 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The benzyloxymethyl protecting group was removed by dissolving the residue in a 4:1 solution of EtOH-HOAc (10 mL) and hydrogenating over palladium black (75 mg) under 1 atm of hydrogen for 24 h. The catalyst was removed by filtration through Celite and the filtrate solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a 50:50:7 by volume mixture of $CHCl_3$, EtOAc, and 4% $NH_4OH$-MeOH as eluant. Two diastereomers were obtained and each was lyophilized from water containing 1% TFA. The title compound is the lower Rf isomer.

Higher $R_f$ Isomer:

Analysis calculated for $(C_{31}H_{44}N_4O_5S_2)\cdot 1.0$ TFA$\cdot 1.1$ $H_2O$
C, 52.45; H, 6.24; N, 7.37
Found: C, 52.69; H, 6.12; N, 7.32

TLC: $R_f$ 0.33 (50:50:7 $CHCl_3$:EtOAc:4%$NH_4OH$-MeOH)
HPLC (method A): retention time 8.96 min
FAB MS: m/z 617 ($M^+ + H$)
$^1H$ NMR (300 MHz, $CDCl_3$): free base: d 7.70 (s, 1H), 7.55 (br d, 1H), 7.15-7.25 (m, 4H), 7.00 (s, 1H), 4.35 (m, 1H), 2.90 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

Lower $R_f$ Isomer:

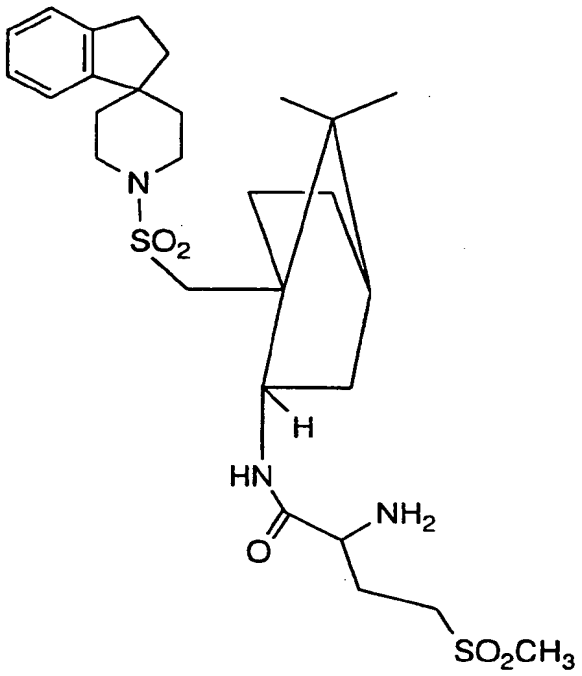
Analysis calculated for $(C_{31}H_{44}N_4O_5S_2)\cdot 1.0$ TFA$\cdot 1.3$ $H_2O$
C, 52.55; H 6.36; N 7.43
Found: C, 52.89; H 6.13; N 7.43

TLC: $R_f$ 0.28 (50:50:7 $CHCl_3$:EtOAc:4%$NH_4OH$-MeOH)
HPLC (method A): retention time 9.15 min

FAB MS: m/z 617 ($M^+ + H$)

$^1H$ NMR (300 MHz, $CDCl_3$): free base: d 7.72 (s, 1H), 7.34 (br d, 1H), 7.15-7.25 (m, 4H), 6.98 (s, 1H), 4.35 (m, 1H), 2.90 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H)

EXAMPLE 65




To a 0°C stirred solution of the product of Example A (1.10 g; 2.74 mmol) in $CHCl_3$ (100 mL) was added DIEA (0.75 mL; 4.3 mmol) and benzyl chloroformate (0.51 g; 3.0 mmol). The solution was stirred at 0°C for 1 h and then at ambient temperature for 14 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 25 mL of a solution of 10:1 MeOH-NH4OH. The mixture was concentrated under reduced pressure, the residue was dissolved in $CHCl_3$ (100 mL) and washed with 5% aqueous HCl (2 x 50 mL) and aqueous $NaHCO_3$ (100 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel

column chromatography using 1:4 EtOAc-hexanes as eluant. The benzyl urethane was obtained as a white foam.

TLC: $R_f$ 0.40 (1:3 EtOAc:hexanes)
HPLC (method A): retention time 12.25 min
FAB MS: m/z 537 ($M^+ + H$)

To a 0°C stirred solution of the benzyl urethane (1.25 g; 2.33 mmol) in DMF (20 mL) was added iodomethane (0.435 mL; 7.00 mmol) and sodium hydride (0.140 mg of a 60% dispersion in mineral oil; 3.50 mmol). The solution was stirrred at 0°C for 1 h and then at ambient temperature for 18 h. The reaction mixture was treated with HOAc (1 mL) and the solvents were removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:5 EtOAc-hexanes as eluant. The N-methyl benzyl urethane was obtained as a white foam.

TLC: $R_f$ 0.34 (1:4 EtOAc:hexanes)
HPLC (method A): retention time 12.71 min
FAB MS: m/z 551 ($M^+ + H$)

To a stirred, argon purged solution of the N-methyl benzyl urethane (1.00 g; 1.82 mmol) in 96:4 MeOH-$HCO_2H$ (25 mL) was added palladium black (0.37 g). The reaction mixture was stirrred for 16 h at ambient temperature. The catalyst was removed by filtration through Celite, and the filtrate solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 $CHCl_3$:MeOH:$NH_4OH$ as eluant. The N-methyl endo-amine product was obtained as a white foam.

TLC: $R_f$ 0.35 (92:8:0.8 $CHCl_3$:MeOH:$NH_4OH$)
HPLC (method A): retention time 7.88 min
FAB MS: m/z 417 ($M^+ + H$)

To a stirred solution of the N-methyl endo-amine (0.650 g; 1.56 mmol) in $CHCl_3$ (50 mL) was added the acid fluoride of Na-Boc-

L-methionine sulfone (510 mg; 1.80 mmol) and DIEA (0.35 mL; 2.0 mmol). The mixture was stirred at ambient temperature for 48 h, and then extracted with 10% aqueous citric acid solution (2 x 30 mL), water (30 mL), and aqueous NaHCO3 (2 x 30 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (10 mL), and to the solution was added TFA (6 mL). The mixture was stirred at ambient temperature for 1.5 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

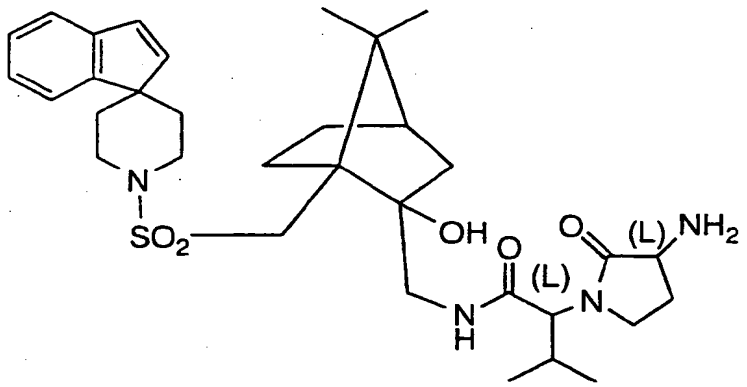
Analysis calculated for $(C_{29}H_{45}N_3O_5S_2)\cdot 0.4$ TFA·0.5 EtOAc
C 57.04 H 7.55 N 6.28
Found: C 57.04 H 7.44 N 6.28
TLC: $R_f$ 0.18 (95:5:0.5 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 9.80 min
FAB MS: m/z 580 ($M^+ + H$)
$^1H$ NMR (300 MHz, $CDCl_3$): d 7.15-7.25 (m, 4H), 5.20 (m, 2H), 3.17 (s, 3H), 2.92 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H)

## EXAMPLE 66

To a stirred solution of endo-(1S)-1'(((2-amino-7,7-dimethylbicyclo(2.2.1)-hept-1-yl)-methyl)-sulfonyl)spiro(1H-indan-1,4'-piperidine (94 mg; 0.17 mmol) in ethanol (20 mL) was added N-(3-bromopropyl)-phthalimide (69 mg; 0.255 mmol) followed by diisopropylethyl amine (0.044 mL; 0.255 mmol). The temperature was then increased to 50°C. After approximately 18 hr the solution was cooled then concentrated under reduced pressure. The residue was dissolved in methylene chloride (150 mL), washed with 1M HCl (2 x 150 mL) then dried over sodium sulfate and concentrated. Purification by flash chromatography (5% methanol in methylene chloride) afforded the title compound (45 mg; 40%) as a white solid.

Analysis calculated for $(C_{39}H_{50}N_4O_6S)\cdot 0.10\ H_2O\cdot 0.15\ CH_2Cl_2$
C, 65.54; H, 7.10; N, 7.81
Found: C, 65.52; H, 7.09; N, 7.71
HPLC: (Vydac C18 Column; gradient from 95/5 to /100 H20/CH3CN with 0.1% TFA. 15 min. gradient, flow rate = 1.5 ml/min.)
$R_t$ = 13.81 min. Purity = 100%
$^1$HNMR: Consistent with structure
FABMS: m/z = 703 ($M^+$ + H)

## EXAMPLE 67




Valine methyl ester (2.5g, 14.9 mmol), t-BOC-methionine (3.73 g,14.9 mmol), HBT (2.01 g, 14.9 mmol) and EDC (2.33g, 14.91 mmol) were suspended in methylene chloride (60ml). The pH of the reaction was adjusted using E. Merck strips to about 9 with Et3N. After stirring overnight at ambient temperature, the reaction was evaporated and the residue was dissolved in ethyl acetate (60ml). The ethyl acetate solution was extracted three times with 5M citric acid (20 ml), three times with 1M sodium bicarbonate (20 ml), one time with water and one time with saturated sodium chloride (20ml). The ethyl acetate solution was then dried over anhydrous sodium sulfate, filtered and evaporated to dryness.

The residue was dissolved in methyl iodide (25ml) and stirred overnight, and the resulting mixture was evaporated to dryness. The resulting methyl sulfonium salt (4.72mmol) was dissolved in a 1:1

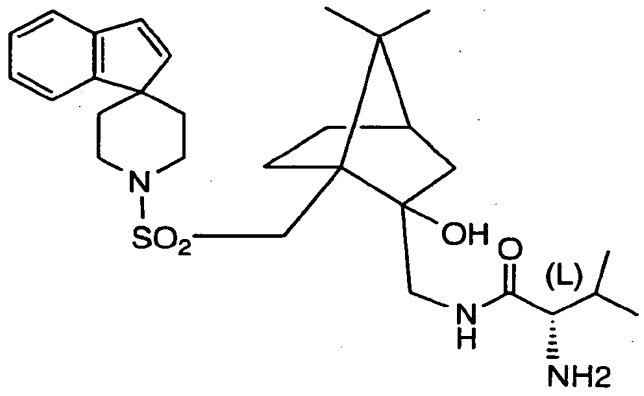
mixture of DMF and methylene chloride (150ml). After cooling to zero degrees in a saltwater/ice bath, sodium hydride (60% in mineral oil: 0.57g, 9.44mmol) was added. After stirring for 3hr, the reaction was treated with glacial acetic acid (1 ml) followed by water (1 ml). The mixture was stirred for 15min. at ambient temperature, then evaporated. The crude product was dissolved in water (150 ml) and neutralized with aqueous sodium bicarbonate. The mineral oil and neutral by-products were removed by extracting three times with methylene chloride (50 ml). The aqueous layer was then acidified with citric acid and extracted three times with methylene chloride (50ml). The combined methylene chloride layers were dried over sodium sulfate, filtered and evaporated. Purification of the crude product was carried out by preparative HPLC using a Waters C-18 column in a SepTech ST/Lab 800C instrument with a water/acetonitrile gradient increasing from 10% to ca. 60% acetonitrile.

The product so obtained (60 mg, 0.20 mmol) was combined with (1S)-1'-(((7,7-dimethyl-(2-endo-aminomethyl-2-exo-hydroxy)-bicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)-spiro-(1H-indene-1,4'-piperidine) (86 mg, 0.20 mmol), HBT (27 mg, 0.20 mmol) and EDC (38 mg, 0.20 mmol) in methylene chloride (10 ml). The pH of the mixture was adjusted to ca. 9 with triethylamine. After stirring overnight, the reaction was evaporated and the residue was dissolved in ethyl acetate (25ml). The ethyl acetate solution was extracted three times with 5M citric acid (2ml), three times with 1M sodium bicarbonate (2ml), one time with water and one time with saturated sodium chloride (2ml). The ethyl acetate solution was then dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The product was dissolved in a 40% solution of trifluoroacetic acid in methylene chloride (3 ml) and stirred for lhr at ambient temperature. The solvent was then evaporated, and the residue was dissolved in methanol and purified by preparative HPLC using the conditions described.

NMR: Consistent with structure

FAB MS: 613 ($M^+ + H$)
HPLC: >99% pure at 214 nM
Analysis calc'd for $C_{33}H_{47}N_4O_5 \cdot 2.0\ C_2HF_3O_2 \cdot 1.4H_2O$:
Calc'd: C, 51.31; H, 6.15; N, 6.47
Found: C, 51.31; H, 6.00; N, 6.66.

## EXAMPLE 68

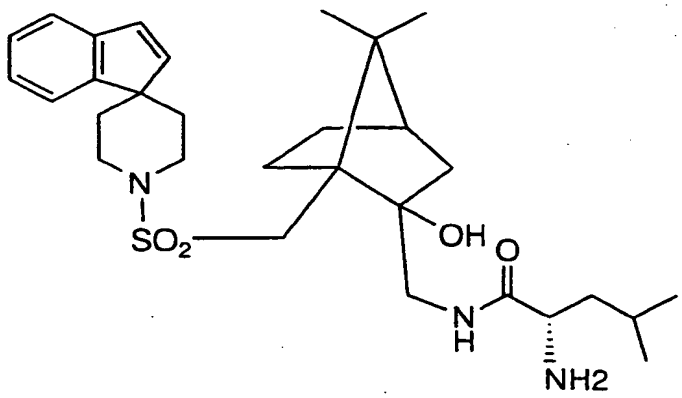



To a solution of (1S)-1'-(((7,7-dimethyl-(2-endo-amino-methyl-2-exo-hydroxy)-bicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)-spiro(1H-indene-1,4"-piperdine (100 mg; 0.23 mmol) in DMF was added t-boc-L-valine (60 mg; 0.28 mmol), 1-hydroxybenzotriazole (37 mg; 0.28 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (53 mg; 0.28 mmol). The pH was adjusted to 9 with triethylamine (96 uL; 0.69 mmol). After stirring for 1.5 hrs., the solution was concentrated to dryness and treated with 5% citric acid solution. This water layer was then basified with saturated sodium bicarbonate and extracted 3 times with ethyl acetate. The organics were combined and dried over sodium sulfate, filtered, and concentrated to yield a white oily foam. This white foam was dissolved in ethyl acetate, cooled to 0°C and treated with saturated sollution of HCl in ethyl acetate. The reaction mixture was stirred for 45 min., purged with $N_2$ for 30 min., and then concentrated to dryness. The resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. The aqueous

layer was extracted 3 times with ethyl acetate, and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 98/2/0.2 of methylene chloride/methanol/ammonium hydroxide) to yield the title compound as a white foam.

m.p.: not available
NMR: consistent with structure
HPLC > 97% pure
MS: MH-530.3 (FAB)]
CHN Analysis calculated for $C_{29}H_{43}N_3O_4S$
C, 65.75; H, 8.18; N, 7.93
Found: C, 65.75; H, 8.18; N, 7.93

## EXAMPLE 69

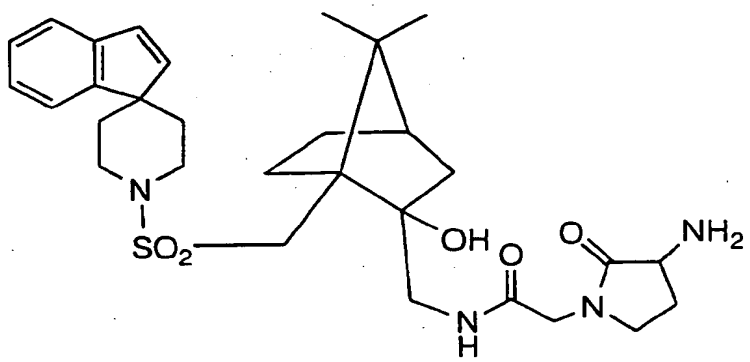



To a solution of (1S)-1'-(((7,7-dimethyl-(2-endo-amino-methyl-2-exo-hydroxy)-bicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)-spiro(1H-indene-1,4"-piperdine) 51 mg; 0.12 mmol) in DMF was added t-boc-L-leucine (36 mg; 0.14 mmol), 1-hydroxybenzotraizole (19 mg; 0.14 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (28 mg; 0.14 mmol). The pH was adjusted to 9 with triethylamine (50 µL, 0.36 mmol). After stirring for 18 hrs., the solution was concentrated to dryness and treated with 5% citric acid solution. The water layer was then basified with saturated sodium bicarbonate and extracted 3 times

with ethyl acetate. The organics were combined and dried over sodium sulfate, filtered, and concentrated to yield a yellow oil. This yellow oil was dissolved in ethyl acetate, cooled to 0°C and treated with a saturated solution of HCl in ethyl acetate. The reaction mixture was stirred for 45 min., purged with $N_2$ for 30 min., and then concentrated to dryness. The resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate the aqueous layer was extracted 3 times with ethyl acetate and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue purified by flash chromatography (eluted with 98/2/0.2 of methylene chloride/methanol/ammonium hydroxide) to yield the title compound as a white foam.

m.p.: 88 - 110° C
NMR: consistent with structure
HPLC: > 98% pure
MS: MH-544.3 (FAB)
CHN Analysis calculated for $C_{30}H_{45}N_3O_4S.0.35H_2O$:
C, 65.50; H, 8.37; N, 7.64
Found: C, 65.48; H, 8.39; N, 7.60

## EXAMPLE 70

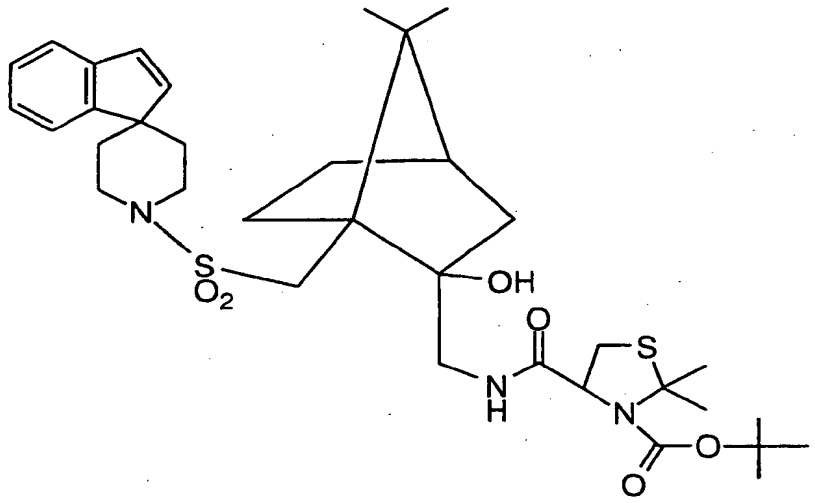


To a solution of (1S)-1'-(((7,7-dimethyl-(2-endo-amino-methyl-2-exo-hydroxy)-bicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)-spiro(1H-indene-1,4"-piperdine) (72 mg; 0.17 mmol) in DMF was

added 2-(3-amino-2-oxopyrrolidin-1-yl)acetic acid (52 mg; 0.20 mmol), 1-hydroxybenzotriazole (27 mg; 0.20 mmol), and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (38 mg; 0.20 mmol). The pH was adjusted to 9 with triethylamine (70 µL; 0.50 mmol). After stirring for 18 hrs., the solution was concentrated to dryness and treated with 5% citric acid solution. The water layer was then basified with saturated sodium bicarbonate and extracted 3 times with ethyl acetate. The organics were combined and dried over sodium sulfate, filtered, and concentrated to yield a yellow oil which was purified by flash chromatography (eluted with 98/2/0.2 of methylene chloride/methanol/ ammonium hydroxide). The product was dissolved in ethyl acetate, cooled to 0°C, and treated with a saturated solution of HCl in ethyl acetate. The reaction mixture was concentrated to dryness. The resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. The aqueous layer was extracted 3 times with ethyl acetate and the organic fractions were combined, and dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 97/3/0.3 of methylene chloride/methanol/ammonium hydroxide) to yield the title compound as a white foam.

m.p.: 115 - 155°C
NMR: consistent with structure
HPLC: > 98% pure
MS: M+H-571 (FAB)
CHN Analysis calculated for $C_{30}H_{42}N_4O_5S.0.85H_2O \cdot 0.25 C_4H_{10}O$:
C, 61.58; H, 7.70; N, 9.27
Found: C, 61.56, H, 7.44; N, 9.23

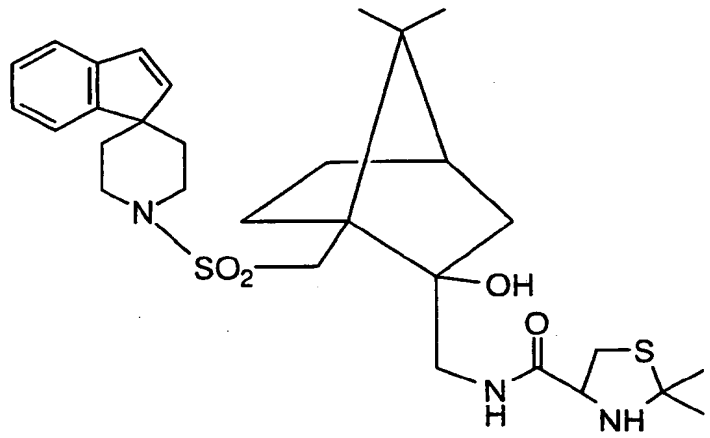
## EXAMPLE 71



Endo (1S)-1'(((2-aminomethyl-7,7-dimethylbicyclo-(2.2.1)hept-1-yl)methyl)sulfonyl)spiro(indene-1,4'-piperidine) (337 mg, 0.78 mmole) and N-isobutyl-oxycarbonyl-5,5-dimethyl-L-thiazolidine-4-carboxylic acid (230 mg, 0.90 mmole) were combined with 438 mg (0.99 mmole) of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorosphosphate in 5 ml of dry dimethyl formamide at room temperature with protection from moisture (calcium sulfate drying tube). The pH of mixture was adjusted to 8.5 with diisopropyl-ethylamine. The resulting solution was allowed to stir at room temperature for two hours. The dimethylformamide was then removed under reduced pressure, and the residue taken up in 150 ml of ethyl acetate and washed with saturated sodium bicarbonate (2 x 25 ml) and brine (1 x 25 ml). The ethyl acetate was dried over sodium sulfate, filtered, and concentrated to give 941 mg of an oil. The analytically pure material was obtained via chromatography on precoated silica gel plates (1.5 mm x 20 x 20 cm) developed with ethyl acetate in hexane (35:65). The product was obtained as an oil.

NMR: consistent with structure
FAB MS: $M^+$+H=574 (Compound minus t-BOC)
Analysis calculated for $C_{35}H_{51}N_3O_6S_2 \cdot 1.3\ CHCl_3$
C, 52.58; H, 5.35; N, 5.07
Found: C, 52.62; H, 6.,40; N, 4.99

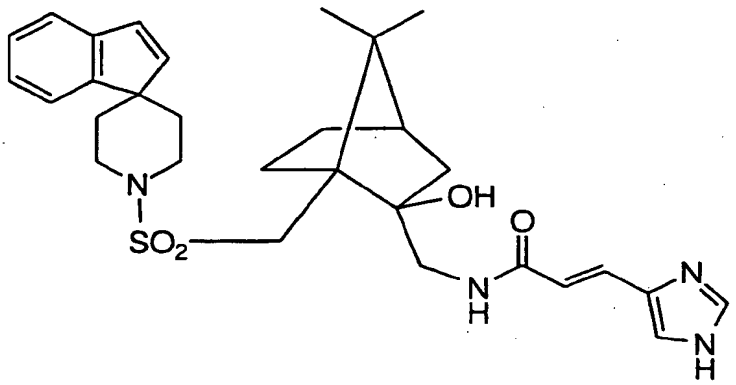
EXAMPLE 72




The product of the preceding Example 71 was dissolved in ethyl acetate, and the solution was cooled to 0°C. HCl (g) was bubbled into the solution for three minutes, and then let stand at 0°C for 30 minutes. The ethyl acetate was removed under vacuum and the residue evaporated twice from ethyl acetate. The residue was chromatographed on precoated silica gel plates 6.5 mm x 20 cm x 20 cm) using chloroform-methanol-ammonium hydroxide (97-3-0.3/v-v-v) to develop the plates. The product was obtained as an amophous solid.

m.p.: 126 - 129°C
NMR: consistent with structure
FAB MS: $M^+$+H = 574.3
Analysis calculated for C30H43N3O4S2•0.15 CHCl3
C, 61.19; H, 7.35; N, 7.10
Found: C, 61.10; H, 7.33; N, 7.12

EXAMPLE 73



To a solution of (1S)-1'-(((7,7-dimethyl-(2-endo-amino-methyl-2-exo-hydroxy)-bicyclo-(2.2.1)-hept-1-yl)-methyl)sulfonyl)-spiro(1H-indene-1,4-piperdine) (108 mg; 0.25 mmol) in degassed DMF was added 4-imidazoleacrylic acid (41.44 mg; 0.30 mmol) and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (132.69 mg; 0.30 mmol). The pH of the reaction mixture was adjusted to 9 with diisopropylethylamine. After stirring for 14 hr, the reaction mixture was concentrated to dryness. The resulting solid was dissolved in methanol and then purified by reverse phase preparative HPLC utilizing a Water C-18 column (45 minute gradient, 5% to 70% acetonitrile/water containing 0.1% trifluoroacetic acid, 13.5 ml/min flow rate). The product containing fractions were combined and lyophilized to give an amorphous white solid.

NMR: consistent with structure;
HPLC: > 97% pure (254 nM)
FAB MS: M+H+ thioglycerol matrix = 659
CHN Analysis calculated for $C_{30}H_{38}N_4O_4S \cdot 1.6CF_3CO_2H$
Calc'd: C, 54.39; H, 5.44; N, 7.64.
Found: C, 54.50; H, 5.20; N, 7.53.

In addition to those compounds specifically exemplified above, additional compounds of the present invention are set forth in tabular form below. These compounds are synthesized by use of the synthetic routes and methods described in the above Schemes and

Examples and variations thereof well known to those of ordinary skill in the art, and not requiring undue experimentation. All variables listed in the Tables below are with reference to the following generic structure:

TABLES

R =

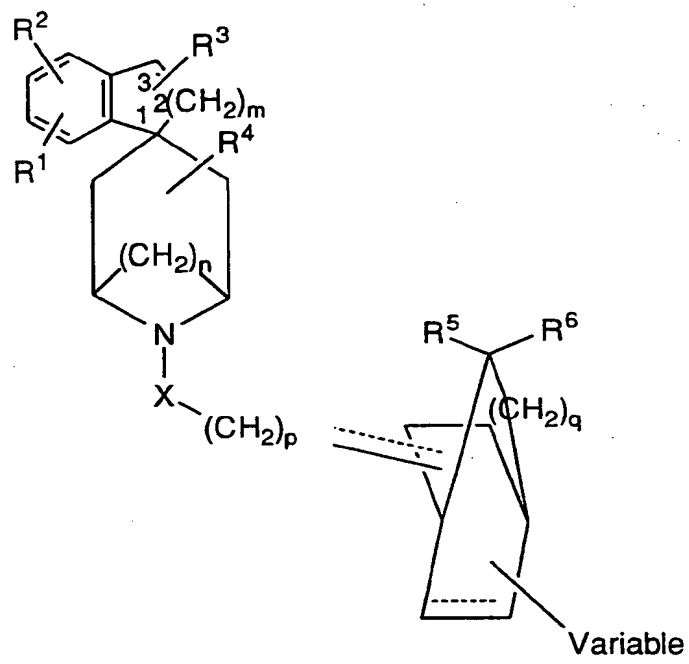


TABLE 1

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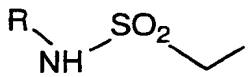

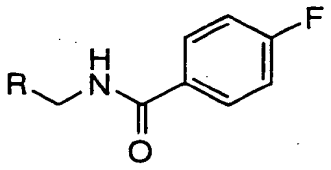

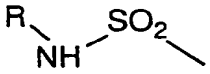

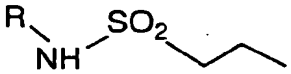

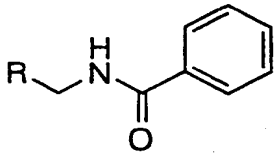

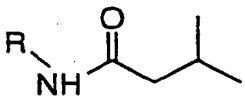

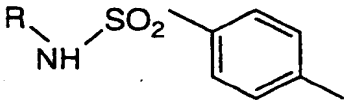

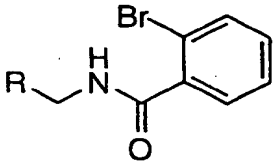

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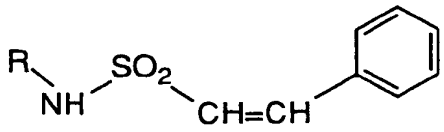

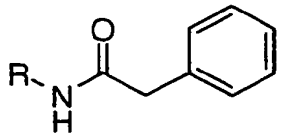

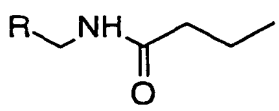

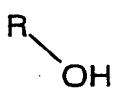

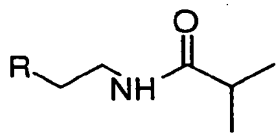

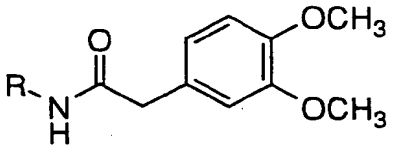

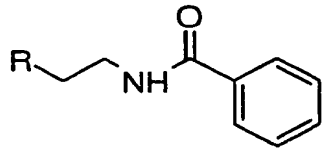

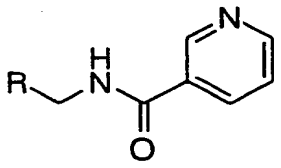

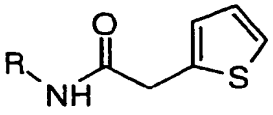

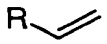

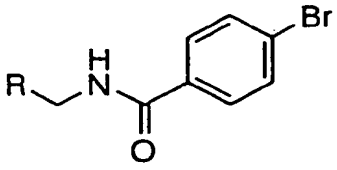

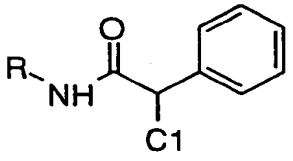

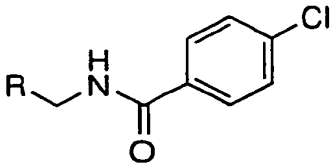

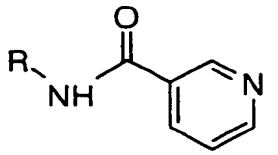

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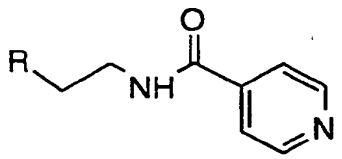
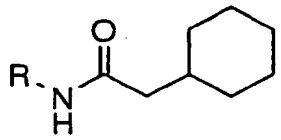
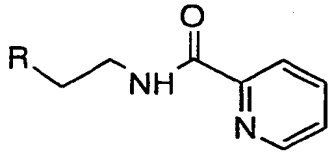
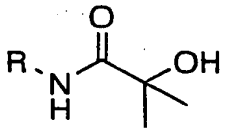
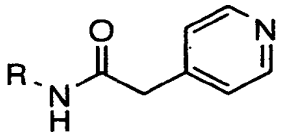
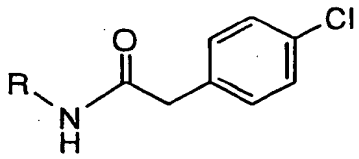


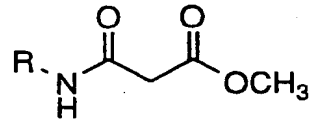


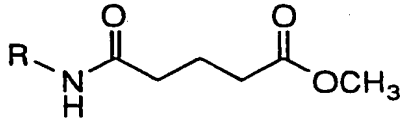


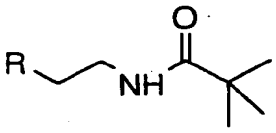












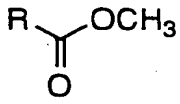
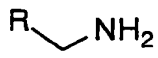
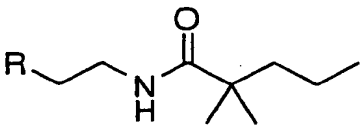
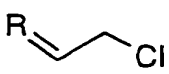
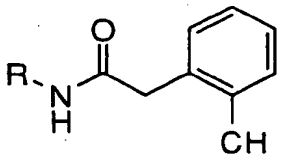


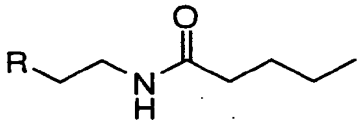
TABLE 2 CONT'D

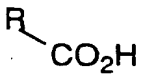


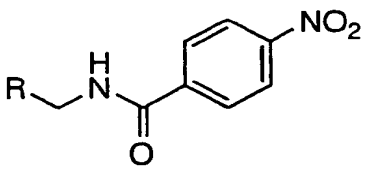


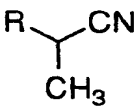


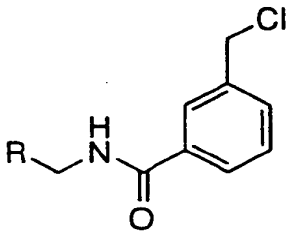












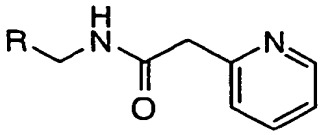
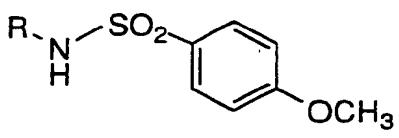
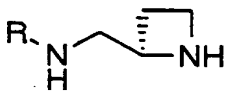
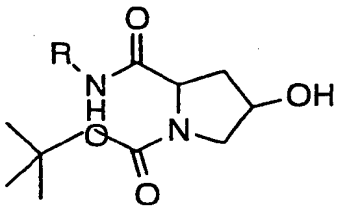
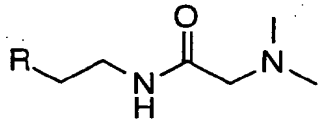


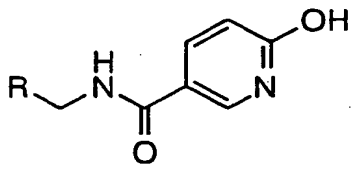
TABLE 3

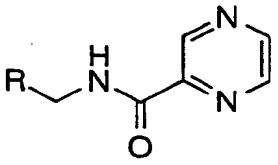


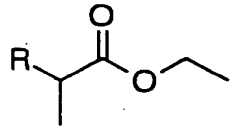


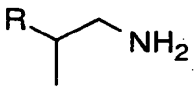


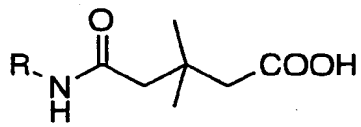


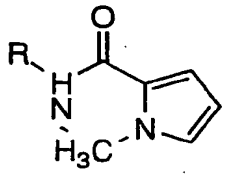












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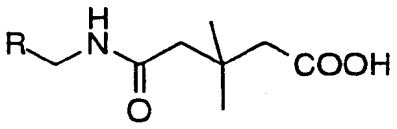
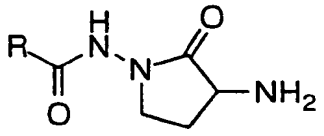
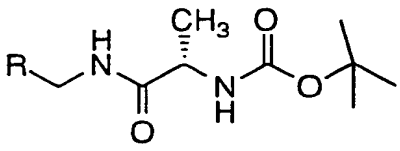
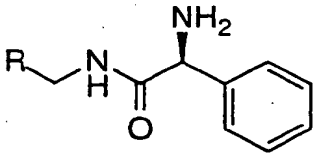
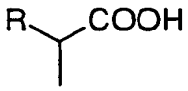
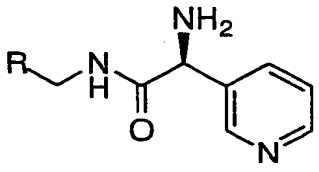


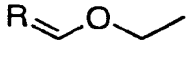












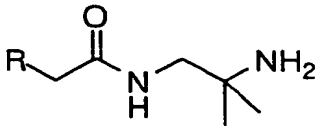
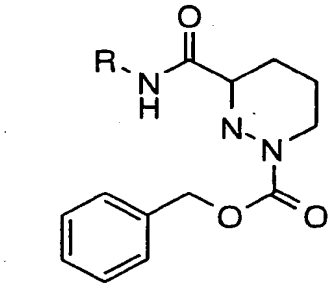
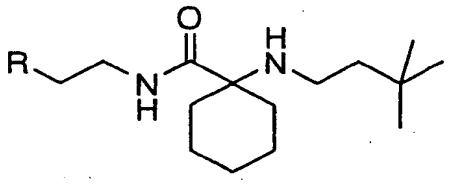
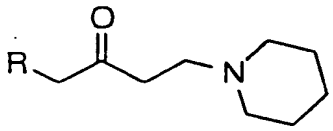
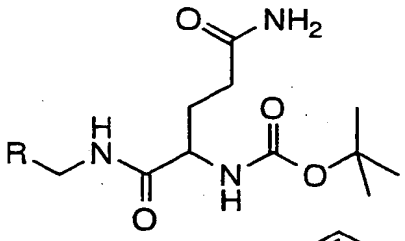


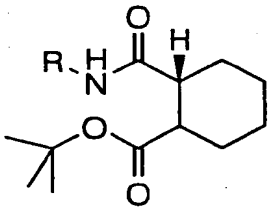
TABLE 4

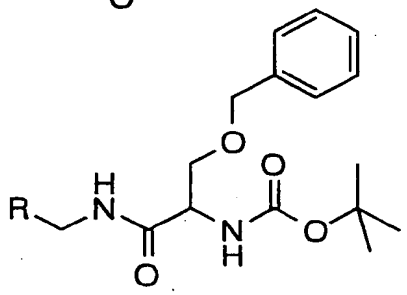


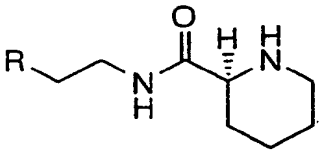


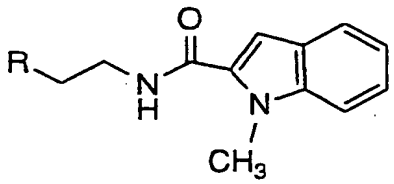












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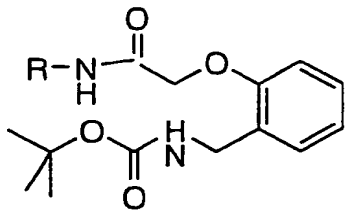

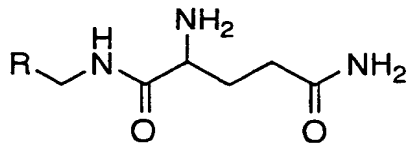

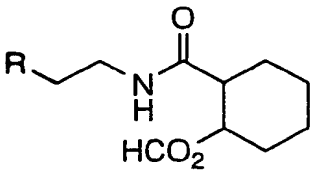

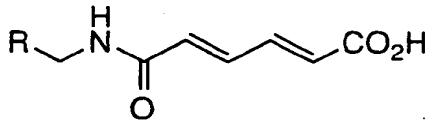

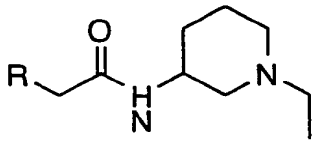

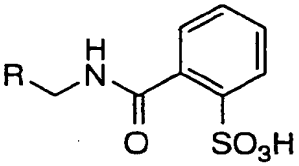

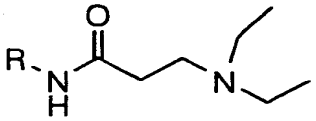

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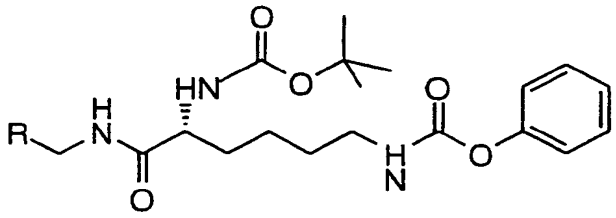

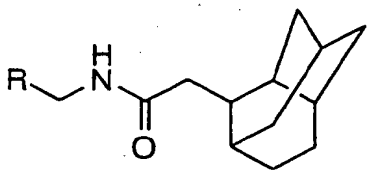

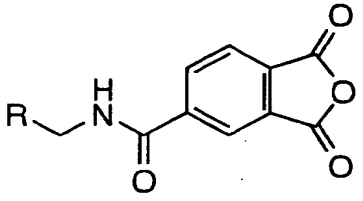

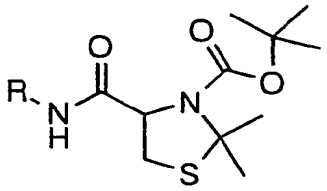

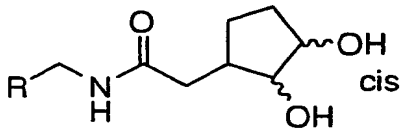


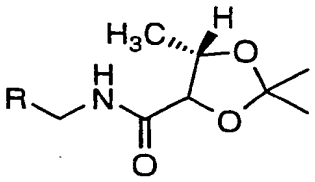

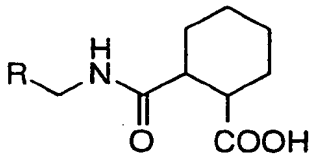

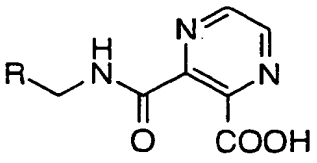

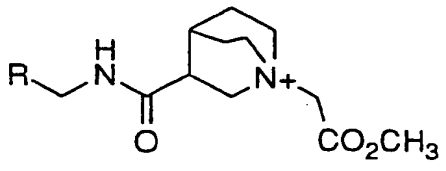

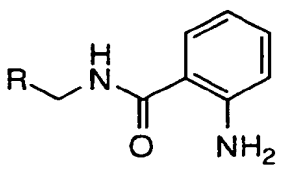

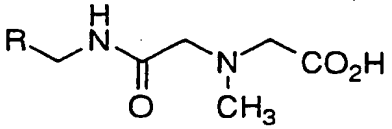

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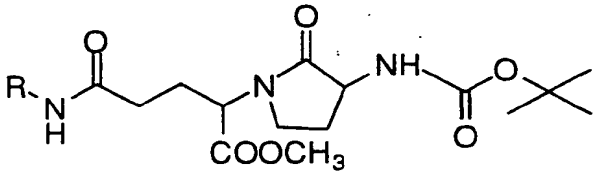

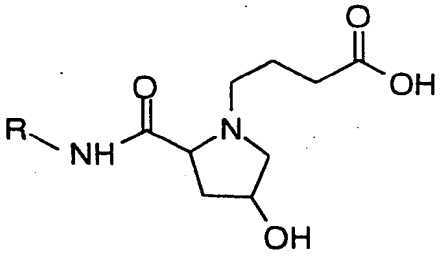

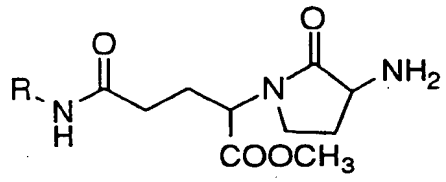

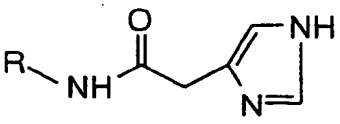

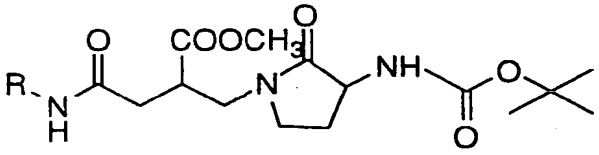

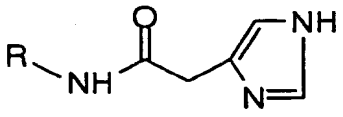

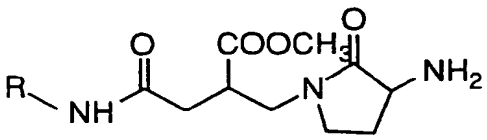

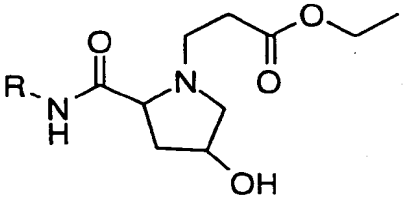

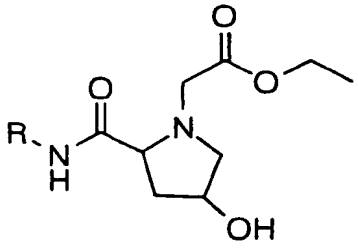

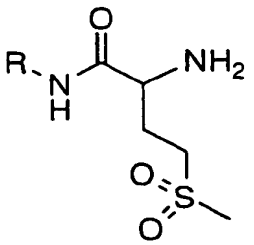

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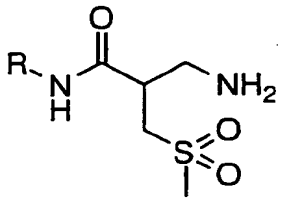

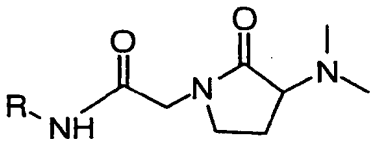

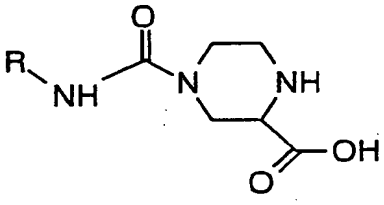

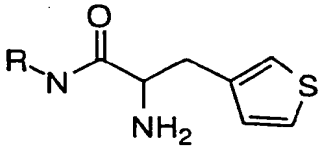

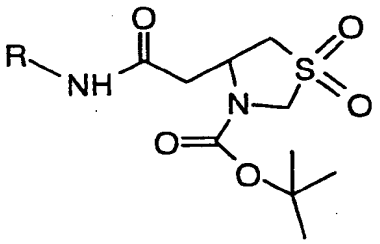

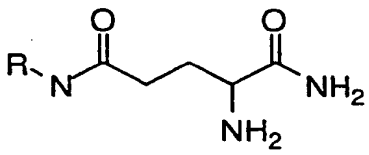

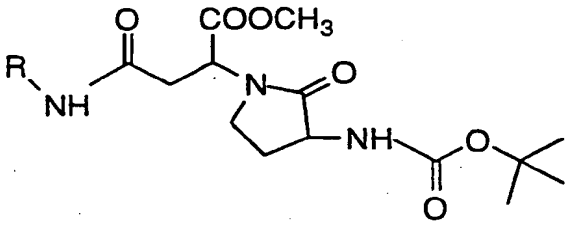

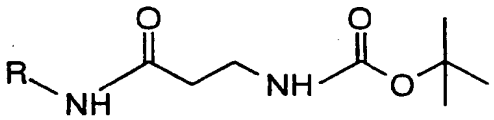

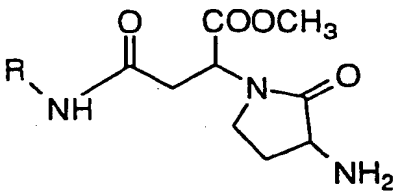

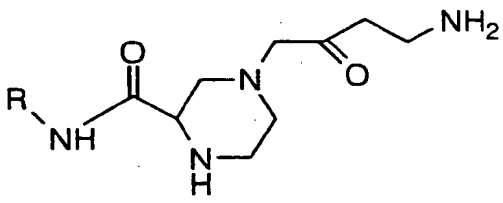

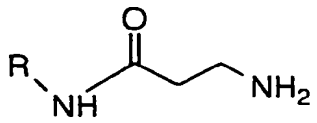

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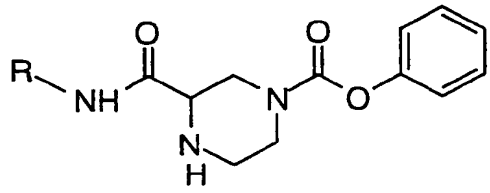

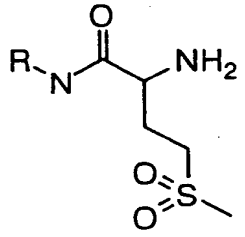

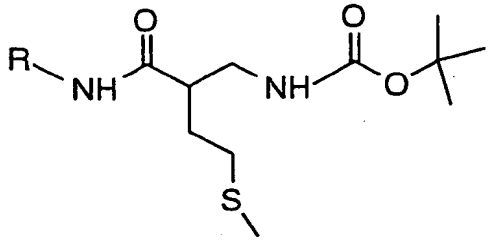

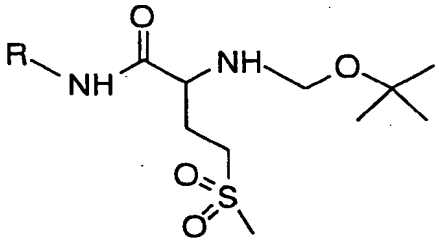

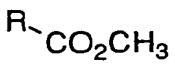

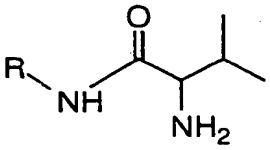

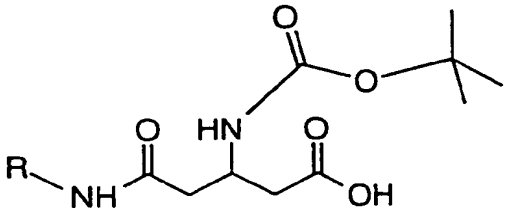

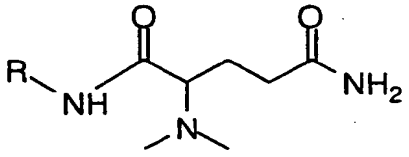

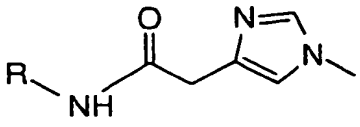

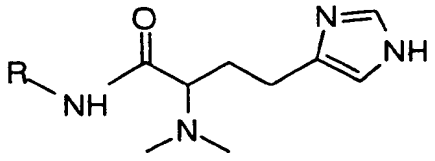

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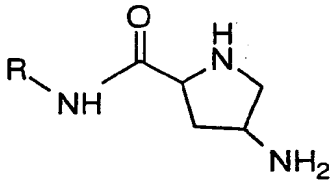
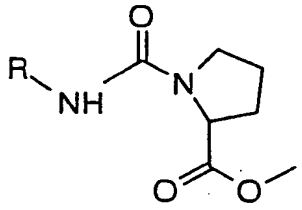
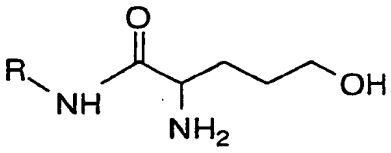
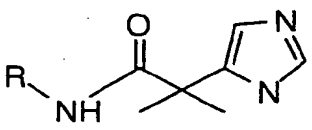
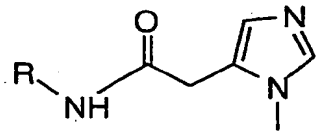
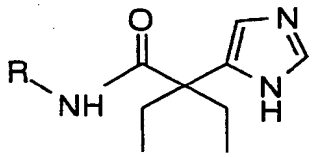


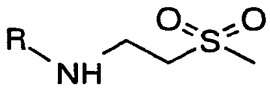


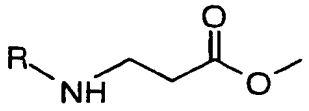


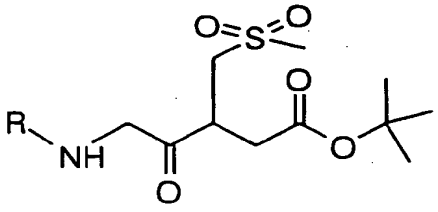


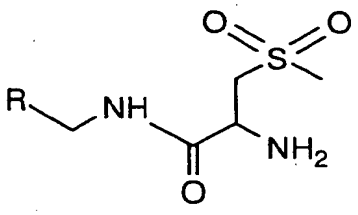












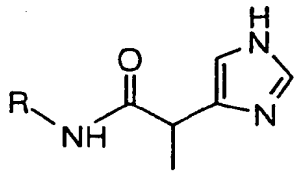
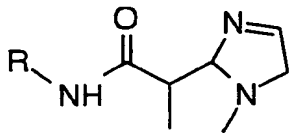
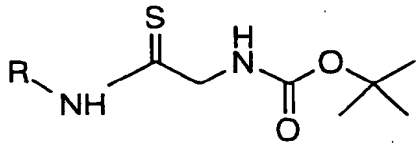
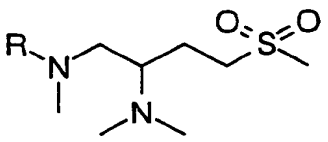
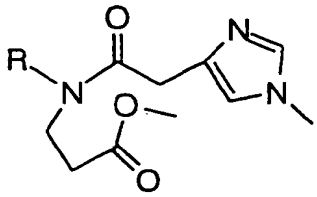


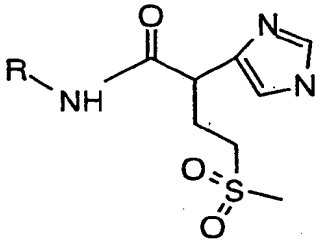
TABLE 10

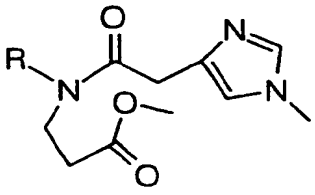


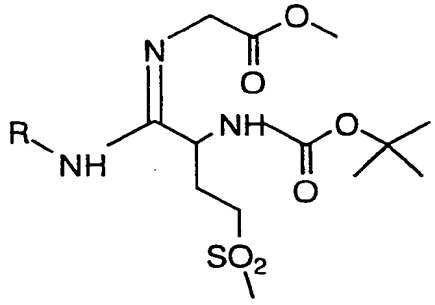


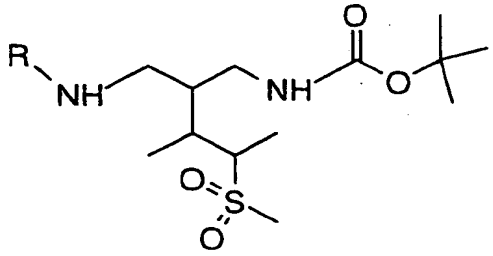


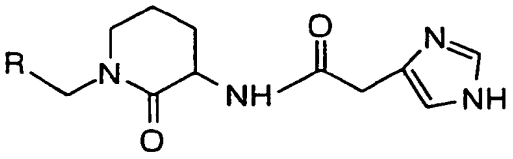


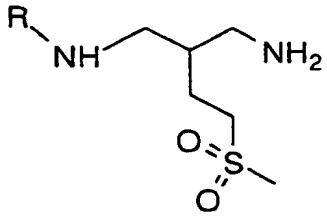












## EXAMPLE 74
## RADIOLIGAND BINDING ASSAYS

The high affinity binding of [$^3$H]oxytocin (OT) to uterine tissue and [$^3$H]arginine vasopressin (AVP) to liver (AVP-$V_{1a}$ site) and kidney (AVP-$V_2$ site) tissue was determined using crude membrane preparations as described previously [Pettibone, D.J., et al., *J. Pharmacol. and Exper. Ther.*, 256(1): 304-308 (1991)]. Uterine tissue was taken from nonpregnant adult Sprague-Dawley rats (Taconic Farms, Germantown, NY) pretreated (18-24 h) with diethylstilbestrol propionate (DES; 300 µg/kg, i.p.). Uterine tissue (full thickness) was also taken with informed consent from nonlabor pregnant women undergoing cesarean section at 38 to 39 weeks gestation (Oregon Health Sciences Center, Portland, OR). Liver and kidney medulla samples were taken from male rats and from human surgical and early postmortem donors (National Disease Research Interchange, Philadelphia PA; Analytical Biological Services, Wilmington, DE).

Competition studies were conducted at equilibrium using 1 nM [$^3$H]OT or 0.5 nM [$^3$H]AVP in the following buffer: 50 mM Tris, 5 mM $MgCl_2$, 0.1% bovine serum albumin. Nonspecific binding was determined using 1 µM unlabeled OT or AVP in their respective assays. The binding reactions were initiated by the addition of tissue preparation and terminated by filtration using a Skatron cell harvester (model 7019, Skatron, Inc., Sterling, VA). Ki values were calculated for each compound using three to six separate $IC_{50}$ determinations ($K_i=IC_{50}/[1- c/K_d]$); [Cheng, Y-C; Prusoff, W.H.; Biochem Pharmacol 22:3099 (1973)] with mean $K_d$ values obtained from replicate (n = 3) equilibrium saturation binding assays (10 point, 100 fold concentration range): [$^3$H]OT rat uterus, 0.69 nM; human myometrium, 1.1 nM; [$^3$H]AVP: rat liver, 0.21 nM; rat kidney, 0.27 nM; human liver, 0.27 nM; human kidney, 1.4 nM. Computer analysis of the saturation assays by EBDA/LIGAND [McPherson, G.A.; Kinetic, Ebda, Ligand, Lowry: A Collection of Radioligand Binding Analysis Programs, Elsevier Science Publishers, Amsterdam (1985)] indicated that both radioligands apparently bound to single sites in all tissues examined. The final

protein concentration for the various tissues in each assay ranged from 150 to 300 μg/ml [Lowry, P.H.; Rosebrough, N.J.; Farr, A.L.; Randall, R.J.; *J. Biol. Chem.*, 193:265-275 (1951)].

$IC_{50}$ values were determined for the [$^3$H]OT and [$^3$H]AVP binding assays by linear regression of the relation log concentration of compound vs. percent inhibition of specific binding. Data is either reported as a given percentage of inhibition at a specified concentration, or if an $IC_{50}$ was calculated, as a nanomolar concentration. Representative $IC_{50}$ values of the compounds of the instant invention for rat [$^3$H]OT are given below.

| Example | Result For [$^3$H]OT |
|---|---|
| 1 | 70% inhib. at 1000nM |
| 2 | 1100nM |
| 3 | 50% inhib. at 1000nM |
| 4 | 620nM |
| 5 | 190nM |
| 6 | 60% inhib. at 1000nM |
| 7 | 54% inhib. at 1000nM |
| 8 | 140nM |
| 9 | 68% inhib. at 1000nM |
| 10 | 140nM |
| 11 | 69% inhib. at 1000nM |
| 12 | 37% inhib. at 100nM |
| 13 | 180nM |
| 14 | 76% inhib. at 1000nM |
| 15 | 160nM |
| 16 | 61nM |
| 17 | 45nM |
| 18 | 52% inhib. at 100nM |
| 19 | 150nM |
| 20 | 50% inhib. at 100nM |
| 21 | 61nM |

| Example | Result For [$^3$H]OT |
|---|---|
| 22 | 58.8nM |
| 25 | 26% inhib. at 10000nM |
| 26 | 34% inhib. at 1000nM |
| 27 | 47nM |
| 28 | 82nM |
| 29 | 31nM |
| 30 | 45nM |
| 32 | 36% inhib. at 10000nM |
| 33 | 30% inhib. at 1000nM |
| 34 | 48% inhib. at 1000nM |
| 35 | 43% inhib. at 1000nM |
| 36 | 67nM |
| 38 | 33% inhib. at 1000nM |
| 39 | 8500nM |
| 40 | 71% inhib. at 10000nM |
| 41 | 120nM |
| 42 | 96.5nM |
| 43 | 4300nM |
| 44 | 39% inhib. at 100nM |
| 45 | 25% inhib. at 100nM |
| 46 | 36% inhib. at 100nM |
| 47 | 4600nM |
| 48 | 90nM |
| 49 | 54nM |
| 50 | 71% inhib. at 1000nM |
| 51 | 84% inhib. at 1000nM |
| 52 | 290nM |
| 67 | 7.6 nM |
| 73 | 45 nM |

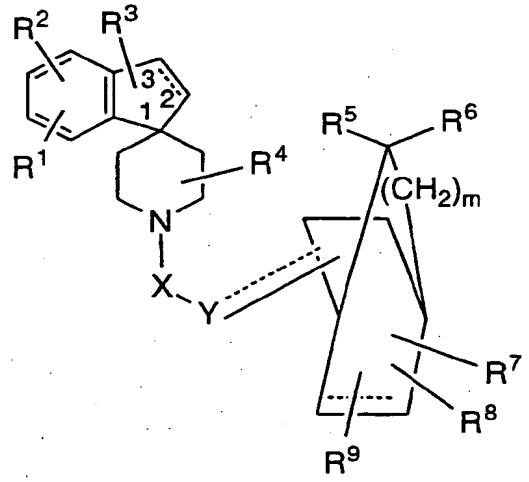
Binding ($K_i$) of compounds to Human OT, Human AVP-$V_{1a}$ and Human AVP-$V_2$:

| Example | OT | AVP-$V_{1a}$ | AVP-$V_2$ |
|---|---|---|---|
| 67 | 3.7 nM | 1.4 nM | 1600 nM |
| 73 | 3.8 nM | 2.7 nM | -- |

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for prevention of preterm labor, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

IN THE CLAIMS:

1. A compound of the formula



wherein
X is

$\overset{O}{\overset{\|}{C}}$,
$CH_2$,
$PO_2H$,
$PO_2Z$ where Z is $C_{1-10}$ alkyl,
$SO_2$,
$SO_2NH$ or
$\overset{O}{\overset{\|}{C}}-NH$;

Y is absent or is
CH or
$CH_2$;

m is an integer of from zero to one;
n is an integer of from zero to five;
p is an integer of from zero to five;

q is an integer of from zero to five;

$R^1$ and $R^2$ are each independently
hydrogen,
halogen,
hydroxy,
$C_{1-10}$ alkyl,
$C_{1-10}$ alkoxy or
trifluoromethyl;

$R^3$ is
hydrogen,
halogen,
hydroxy or
oxo with the proviso that when $R^3$ is oxo then the 2,3 bond is saturated;

R4 is
hydrogen,
phenyl, or
$C_{1-10}$ alkyl,

$R^5$ and $R^6$ are independently
hydrogen,
$C_{1-10}$ alkyl or
$C_{1-10}$ hydroxyalkyl; or

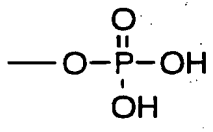
$R^5$ and $R^6$ together are
oxo or
unsubstituted or substituted $C_{3-6}$ cycloalkyl, where said substituents are
hydroxy,
$C_{1-10}$ alkyl,
$C_{1-10}$ hydroxyalkyl,

$C_{1-10}$ alkoxy or
$C_{1-3}$ alkoxyalkoxyalkoxyalkyl;

$R^7$ and $R^8$ are independently
hydrogen or
hydroxyl; or

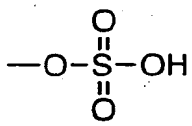
$R^7$ and $R^8$ are, together with the carbons to which they are attached, joined to form a 5-membered heterocyclic ring containing 2 hetero atoms where said hetero atoms are N and O;

$R^9$ is
$C_{7-10}$ alkoxy,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkoxycarbonylalkylaminocarbonyl,
cyano,



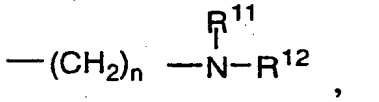
,

$C_{1-10}$ alkyl substituted phosphonate,



,

$C_{1-10}$ alkyl substituted sulfonate,



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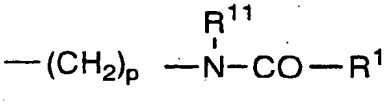

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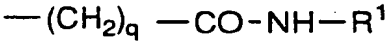


, or
unsubstituted or substituted $C_{1-10}$ alkyl where said substituent is
$R^{10}$;

$R^{10}$ is
hydroxyl,
carboxyl,
$C_{1-10}$ alkoxy,
$C_{1-10}$ alkoxycarbonyl,
$R^{15}$ or
cyano;

$R^{11}$ is
hydrogen,
$C_{1-10}$ alkyl,
$C_{1-10}$ carboxyalkyl or
$C_{1-10}$ alkoxycarbonylalkyl;

$R^{12}$ is
hydrogen,
$C_{1-10}$ alkylsulfonyl,
$C_{1-10}$ alkarylsulfonyl,
$C_{1-10}$ aralkylsulfonyl,
$C_{1-10}$ alkoxyarylsulfonyl,
aminosulfonyl,
$C_{1-10}$ alkylaminosulfonyl,
$C_{1-10}$ dialkylaminosulfonyl,
unsubstituted or substituted $C_{4-15}$ cycloalkylalkyl, bicycloalkyl or tricycloalkyl where said substituent is
oxo or
sulfonyl substituted by unsubstituted or substituted $C_{7-15}$ cycloalkyl, bicycloalkyl or tricycloalkyl where said substituents are
oxo,
oxime or
hydroxy;

$R^{13}$ is

amino,
$C_{1-10}$ alkylamino,
$C_{1-10}$ alkyl which is unsubstituted or mono- or di-substituted by $R^{16}$,
$C_{2-10}$ alkenyl which is unsubstituted or substituted by $R^{16}$,
phenyl substituted by $R^{17}$,
unsubstituted or substituted $C_{3-8}$ cycloalkyl where said substituents are
$C_{1-10}$ alkyl or
carboxy,
N disubstituted by $C_{1-10}$ alkyl,
unsubstituted or substituted $C_{7-15}$ bicycloalkyl or tricycloalkyl where said substituent is
carboxy,
$C_{1-10}$ alkoxy or
$R^{18}$;

$R^{14}$ is
$C_{1-10}$ alkyl,
$C_{1-10}$ aminoalkyl,
$C_{1-10}$ alkoxycarbonylalkyl, or
$C_{1-10}$ carboxyalkyl,

$R^{15}$ is
unsubstituted or substituted 5 membered heterocyclic rings containing 1 hetero atom where said hetero atom is N and said substituents are
oxo,
amino,
$C_{1-10}$ alkylamino,
$C_{1-10}$ carboxyalkylcarbonylamino,
$C_{1-10}$ dicarboxyalkylamino or
$C_{1-10}$ alkyloxycarbonylalkylamino;

$R^{16}$ is

unsubstituted or substituted $C_{4-8}$ cycloalkyl where said substituents are

hydroxy or

carboxy,

$C_{10-15}$ bi- or tricycloalkyl,

halogen,

hydroxy,

carboxy,

oxo,

oxime,

$C_{1-10}$ alkylthio,

$C_{1-10}$ alkylsulfinyl,

$C_{1-10}$ alkylsulfonyl,

$C_{1-10}$ alkoxycarbonyl,

$R^{20}$,

$R^{21}$,

amino,

aminocarbonyl,

$C_{1-10}$ dialkylaminocarbonyl,

$C_{1-10}$ alkylamino,

$C_{1-10}$ dialkylamino,

$C_{1-10}$ alkylcarbamate,

$C_{1-10}$ alkylcarbonate,

$C_{1-10}$ alkylureide,

$C_{1-10}$ aralkylcarbamate,

unsubstituted or substituted aryloxy where said substituents are

amino,

$C_{1-10}$ alkyl or

$C_{1-10}$ aminoalkyl,

$C_{1-10}$ aralkoxy,

unsubstituted or substituted $C_{1-10}$ alkaryloxy where said substituent is

$C_{1-10}$ alkylcarbamate,
N disubstituted by $C_{1-10}$ alkyl and $C_{1-10}$ carboxyalkyl or
N tri-substituted by two $C_{1-10}$ alkyls and by $C_{1-10}$ alkoxycarbonylalkyl with the proviso that a trifluoroacetic acid counterion be present;

$R^{17}$ is
amino,
halogen,
$C_{1-10}$ alkyl,
$C_{1-10}$ alkoxy,
nitro,
phenylcarbonyl or
unsubstituted or substituted 5 membered heterocyclic rings containing 1 hetero atom where said hetero atom is O and wherein said substituent is
oxo;

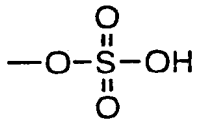
$R^{18}$ is unsubstituted or substituted heterocyclic rings selected from
azetidinyl,
pyrrolidinyl,
pyrrolyl,
piperidinyl,
piperizinyl,
pyridinyl,
pyrimidinyl,
tetrahydrofuranyl,
furanyl,
dioxolanyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrooxazolyl; where said substituents are one or more of
oxo,
hydroxy,

carboxy,
amino,
$C_{1-10}$ carboxyalkyl,
$C_{1-10}$ alkyl,
$C_{1-10}$ alkoxy,
$C_{1-10}$ aralkoxy,
$C_{1-10}$ alkaryloxy,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkoxycarbonylamino,
$C_{1-10}$ alkoxycarbonylalkyl,
$C_{1-10}$ aralkoxycarbonyl or
substituted or unsubstituted phenyl where said substituents are
$C_{1-5}$ alkyl,
carboxy or
halogen;

$R^{20}$ is unsubstituted or substituted heterocyclic rings selected from
azetidinyl,
pyrrolidinyl,
pyrrolyl,
tetrahydroimidazolyl,
imidazolyl,
tetrazolyl,
piperidinyl,
pyridinyl,
hexahydroazepinyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrothiazinyl; where said substituents are one or more of
$C_{1-10}$ alkyl,
$C_{1-10}$ aralkyl,
$C_{1-10}$ aralkoxy,

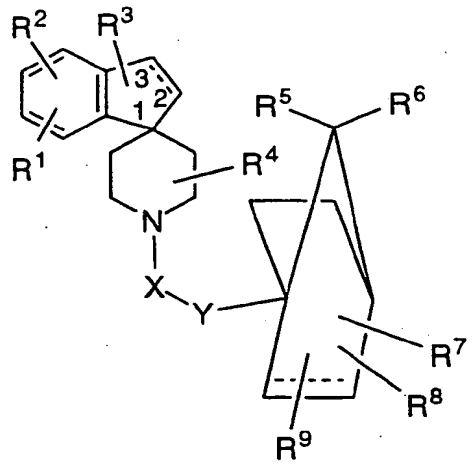
$C_{1-10}$ alkaryl,
amino,
$C_{1-10}$ alkylamino,
$C_{1-10}$ dialkylamino,
oxo,
oxime,
fused phenyl,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkylcarbonate,
$C_{1-10}$ alkylureide,
$C_{1-10}$ alkylcarbamate, or
unsubstituted or substituted 5-membered heterocyclic rings having 1 hetero atom where said hetero atom is N and said substituent is one or more of
oxo or
fused phenyl;

$R^{21}$ is
unsubstituted or substituted phenyl where said substituents are
halogen,
$C_{1-10}$ alkyl,
$C_{1-10}$ carboxyalkyl,
$C_{1-10}$ alkoxy,
5- or 6-membered heterocyclic rings having 1 or 2 hetero atoms where said hetero atoms are N or S,
hydroxy,
carboxy or



and the pharmaceutically acceptable salts thereof.

2. The compound as claimed in Claim 1, of the formula




wherein

X is

O
||
C,

$CH_2$,

$PO_2H$,

$PO_2Z$ where Z is $C_{1-10}$ alkyl, or

$SO_2$;

$R^1$ and $R^2$ are each independently

hydrogen,

halogen or

$C_{1-10}$ alkyl;

R4 is

hydrogen or

phenyl;

$R^5$ and $R^6$ are independently

hydrogen or

$C_{1-10}$ alkyl; or

$R^5$ and $R^6$ together are

oxo or

unsubstituted or substituted $C_{3-6}$ cycloalkyl, where said substituents are

hydroxy,

$C_{1-10}$ hydroxyalkyl or

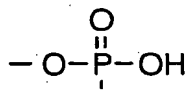
$C_{1-3}$ alkoxyalkoxyalkoxyalkyl;

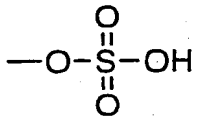
$R^9$ is

$C_{7-10}$ alkoxy,

$C_{1-10}$ alkoxycarbonyl,

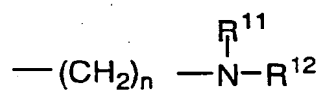
$C_{1-10}$ alkoxycarbonylalkylaminocarbonyl,

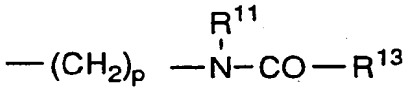
$C_{1-10}$ alkyl substituted  ,

 ,

phosphonate,

$C_{1-10}$ alkyl substituted sulfonate,

 ,

 ,

unsubstituted or substituted $C_{1-10}$ alkyl where said substituent is $R^{10}$;

$R^{12}$ is

hydrogen,

$C_{1-10}$ alkylsulfonyl,

$C_{1-10}$ alkarylsulfonyl,

$C_{1-10}$ alkoxyarylsulfonyl,
aminosulfonyl,
$C_{1-10}$ dialkylaminosulfonyl,
unsubstituted or substituted $C_{3-15}$ cycloalkylalkyl where said substituent is
oxo or
sulfonyl substituted by unsubstituted or substituted $C_{3-15}$ cycloalkyl where said substituent is
oxo;

$R^{14}$ is
$C_{1-10}$ alkyl,
$C_{1-10}$ aminoalkyl or
$C_{1-10}$ alkoxycarbonylalkyl;

$R^{16}$ is
unsubstituted or substituted $C_{5-6}$ cycloalkyl where said substituent is
hydroxy,
$C_{10-15}$ tricycloalkyl,
halogen,
hydroxy,
carboxy,
oxo,
$C_{1-10}$ alkylthio,
$C_{1-10}$ alkylsulfonyl,
$C_{1-10}$ alkoxycarbonyl,
$R^{20}$,
$R^{21}$,
amino,
$C_{1-10}$ alkylamino,
$C_{1-10}$ dialkylamino,
$C_{1-10}$ alkylcarbamate,
$C_{1-10}$ aralkylcarbamate,

unsubstituted or substituted aryloxy where said substituents are
amino,
$C_{1-10}$ alkyl or
$C_{1-10}$ aminoalkyl,
$C_{1-10}$ aralkoxy,
unsubstituted or substituted $C_{1-10}$ alkaryloxy where said substituent is
$C_{1-10}$ alkyl carbamate,
N disubstituted by $C_{1-10}$ alkyl and $C_{1-10}$ carboxyalkyl; or
N tri-substituted by two $C_{1-10}$ alkyls and by $C_{1-10}$ alkoxycarbonylalkyl with the proviso that a counterion be present from the group consisting of $C_{1-5}$ halogenated carboxylic acids;

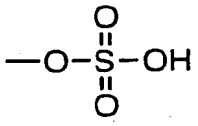
$R^{18}$ is unsubstituted or substituted heterocyclic rings selected from
azetidinyl,
pyrrolidinyl,
pyrrolyl,
piperidinyl,
piperizinyl,
pyridinyl,
pyrimidinyl,
tetrahydrofuranyl,
furanyl,
dioxolanyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrooxazolyl, where said substituents are one or more of
oxo,
hydroxy,
carboxy,
$C_{1-10}$ carboxyalkyl,
$C_{1-10}$ alkyl,

$C_{1-10}$ alkoxy,
$C_{1-10}$ aralkoxy,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkoxycarbonylalkyl or
$C_{1-10}$ aralkoxycarbonyl;

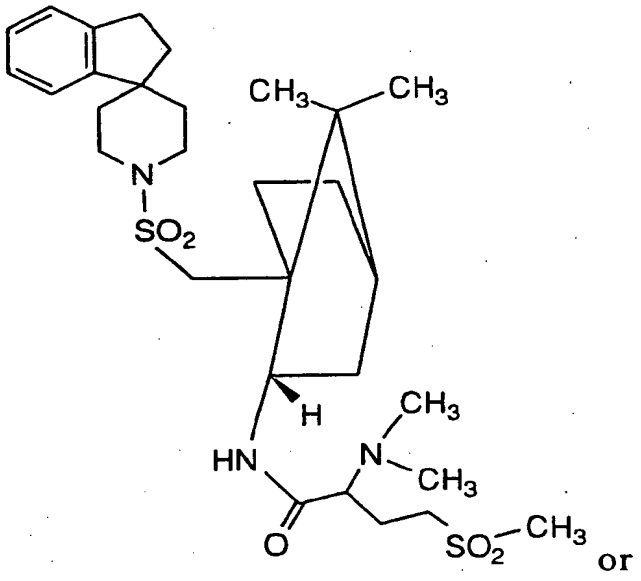
$R^{20}$ is unsubstituted or substituted heterocyclic rings selected from
hexahydroazepinyl,
pyrrolidinyl,
pyrrolyl,
tetrahydroimidazolyl,
imidazolyl,
tetrazolyl,
piperidinyl,
pyridinyl,
azetidinyl,
thienyl,
1, 3-thiazolidinyl or
tetrahydrothiazinyl; where said substituents are one or more of
$C_{1-10}$ alkyl,
$C_{1-10}$ aralkyl,
$C_{1-10}$ aralkoxy,
amino,
oxo,
fused phenyl,
$C_{1-10}$ alkoxycarbonyl,
$C_{1-10}$ alkylcarbamate, or
unsubstituted or substituted 5-membered heterocyclic rings having 1 hetero atom where said hetero atom is N and said substituent is
oxo or
fused phenyl;

$R^{21}$ is

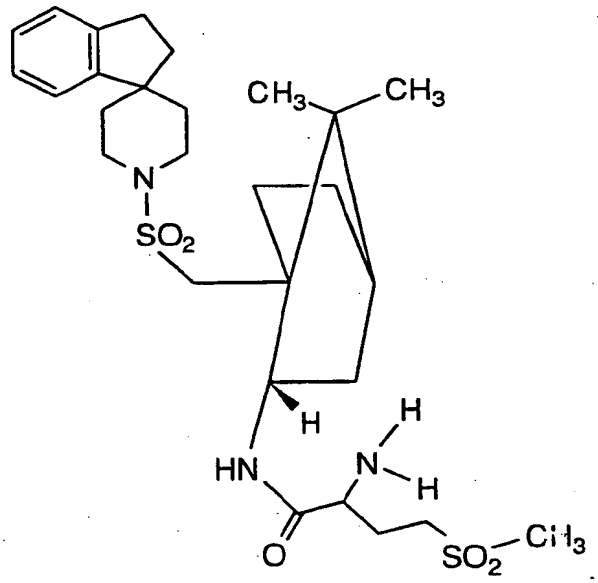
unsubstituted or substituted phenyl where said substituents are
$C_{1-10}$ alkyl,
$C_{1-10}$ carboxyalkyl,
$C_{1-10}$ alkoxy,
5- or 6-membered heterocyclic rings having 1 or 2 hetero atoms where said hetero atoms are N or S,
hydroxy,
carboxy or



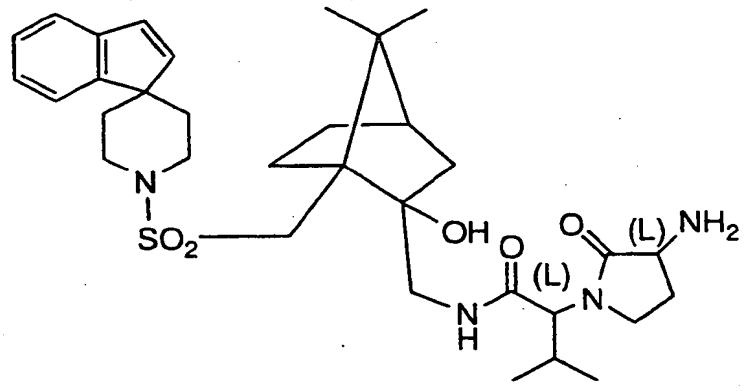
3. The compound of Claim 2, selected from



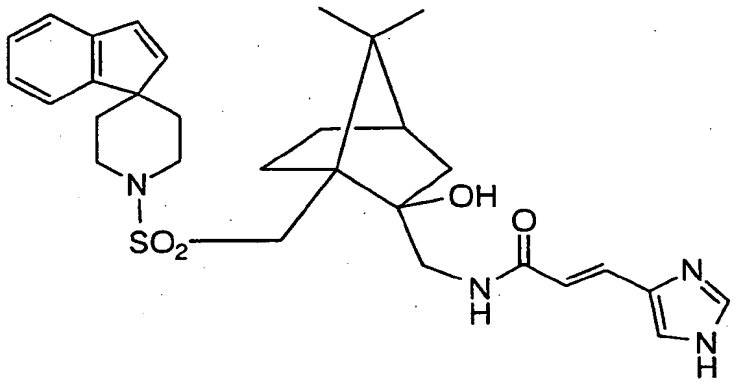
or



4. The compound of Claim 2, selected from



or



5. A pharmaceutical composition, comprising a compound as claimed in Claim 1 in a pharmacologically effective amount for antagonizing the binding of oxytocin to its receptor site, and a pharmaceutically acceptable carrier.

6. A method of preventing preterm labor in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 1.

7. A method of treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 1.

8. A method of stopping labor preparatory to cesarean delivery in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 1.

9. A method of antagonizing the binding of oxytocin to its receptor site in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 1.

10. A method of antagonizing vasopressin from binding to its receptor site in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 1.

11. A method of inducing vasodilation in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

12. A method of treating hypertension in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

13. A method of inducing diuresis in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

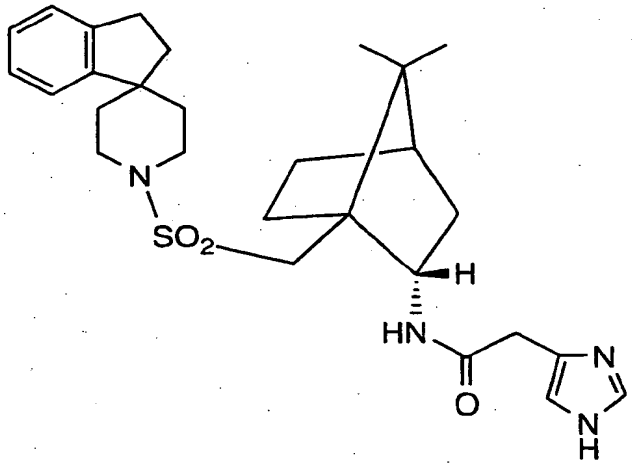
14. A method of inhibiting platelet agglutination in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of the compound as claimed in Claim 1.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of a compound as claimed in Claim 4.

16. A method of preventing preterm labor in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 4.

17. A method of treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 4.

18. A compound of the formula




and the pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition, comprising the compound as claimed in Claim 18 in a pharmacologically effective amount for antagonizing the binding of oxytocin to its receptor site, and a pharmaceutically acceptable carrier.

20. A method of preventing preterm labor in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 18.

21. A method of treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in

Claim 18.

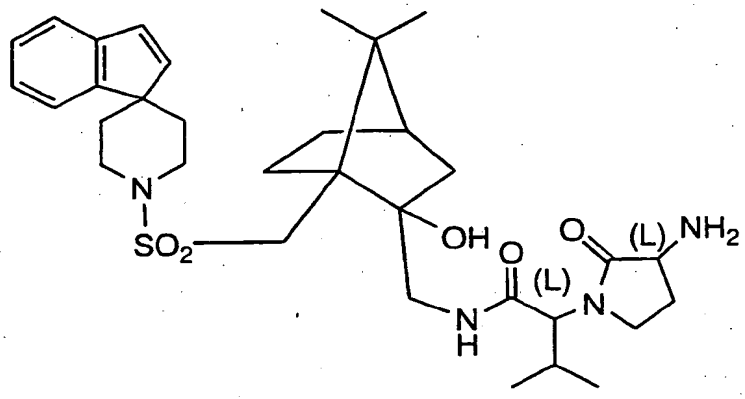
22. A method of stopping labor preparatory to cesarean delivery in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 18.

23. A method of antagonizing the binding of oxytocin to its receptor site in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 18.

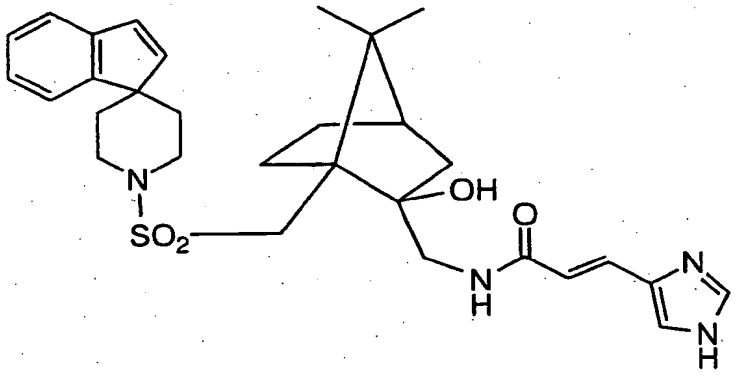
24. A method of treating preterm labor in a mammal in need thereof, comprising administering to said mammal a pharmacologically effective amount of a compound which binds to a human oxytocin receptor with a binding affinity which is no more than ten-fold higher or ten-fold lower than the binding affinity with which the compound binds to a human arginine-vasopressin-$V_1$ (AVP-$V_{1a}$) receptor.

25. The method of Claim 24, wherein the compound binds to the human oxytocin receptor with a binding affinity which is no more than five-fold higher or five-fold lower than the binding affinity with which the compound binds to the human AVP-$V_{1a}$ receptor.

26. The method of Claim 25, wherein the compound is selected from



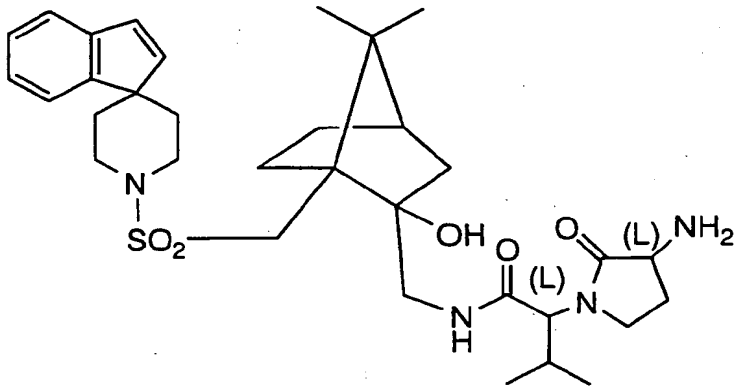
or



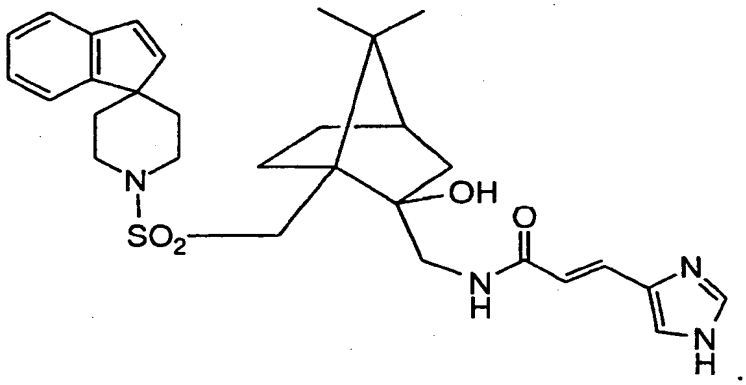
27. A method of treating dysmenorrhea in a mammal in need thereof, comprising administering to said mammal a pharmacologically effective amount of a compound which binds to a human oxytocin receptor with a binding affinity which is no more than ten-fold higher or ten-fold lower than the binding affinity with which the compound binds to a human arginine-vasopressin-V1 (AVP-V1a) receptor.

28. The method of Claim 27, wherein the compound binds to the human oxytocin receptor with a binding affinity which is no more than five-fold higher or five-fold lower than the binding affinity with which the compound binds to the human AVP-V1a receptor.

29. The method of Claim 28 , wherein the compound is selected from



or



# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13483

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.
US CL :546/17; 514/278

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/17; 514/278

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>--<br>Y<br>--<br>A | US, A, 5,204,349 (Bock et al.) 20 APRIL 1993, see formula I. | 1, 2, 5-12, 15-17<br>---<br>3-4, 18-23, 26, 29<br>---<br>13, 14 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date f the actual completion of the international search<br>14 FEBRUARY 1995 | Date f mailing f the international search report<br>13 MAR 1995 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>MARK L. BERCH aco<br>Telephone No. (703) 308-1235 |

Form PCT/ISA/210 (second sheet)(July 1992)*

# INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/US94/13483

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>--<br>Y<br>--<br>A | US, A, 5,091,387 (Evans et al.) 25 February 1992, see Examples 9-11, 13-15, 18-21, 26. | 1, 2, 5-12, 15-17<br>---<br>4, 18-23, 26, 29<br>---<br>3, 13, 14 |
| X | EP, A, 0,486,280 (Freidinger et al.) 20 MAY 1992, see entire document. | 1-23, 26, 29 |
| X<br>--<br>Y<br>--<br>A | EP, A, 0,533,244 (Bock et al.) 24 MARCH 1993, see page 4 and examples. | 1, 2, 5-12, 15-17<br>---<br>3-4, 18-23, 26, 29<br>---<br>13, 14 |
| X<br>--<br>A | EP, A, 0,533, 243 (Gilbert et al.) 24 MARCH 1993, see page 4 and examples. | 1, 2, 5-12, 15-17<br>---<br>3, 4, 13, 14, 18-23, 26, 29 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13483

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07F 9/36; C07D 221/20, 227/12, 227/087, 401/12, 401/14; A61K 31/445, 31/675

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13483

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 27-28, 24, 25
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

It cannot be determined what the scope of the embraced compounds is. No structural requirements of any type are given; the functional requirement is unsearchable.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.